A STUDY OF THE MYOCARDIUM

Based on the histological examination of one hundred and thirty-six hearts obtained at autopsy examinations and a series of animal experiments.

Volume I : Thesis text, references and tables.

Volume II : Case records and autopsy summaries.

Volume III : Illustrations.

A Thesis for the Degree of Doctor of Medicine of the University of Edinburgh

by

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Introduction

This work started as a result of a growing dissatisfaction with the classical methods of examining the heart at and after autopsy. The assessment of heart size by weighing the heart after opening the chambers, and measuring the thickness of the walls was palpably inaccurate; it was suspected that the examination of more than the routine two or three blocks of myocardium would reveal a more accurate incidence of pathological changes in the heart; and finally, the routine methods of histological technique adequate for most tissues, were considered not entirely suitable for the traditionally "difficult" myocardium.

With the encouragement of Professor A.C.Lendrum, in 1956, a start was made to develop staining methods to demonstrate myocardial cellular detail. The experience gained in this project soon raised problems of technical artefact, so that finally the whole tissue processing sequence from the cutting of the blocks from the heart, to the stage of mounting the section for examination was re-examined. It cannot be over-emphasised that the critical examination of the myocardium is dependent upon high standards of histological technique in which traditional methods have a limited

part to play.

During the developmental stage of the technical research, it was confirmed that in general the more blocks of the heart that are examined, the more that is revealed. Many of the lesions seen were suspected to be of hypoxic origin, and thus, having developed the phloxin milling yellow staining sequence and settled on the best available methods of fixation, dehydration and embedding, it was decided to survey a series of unselected routine hearts by the application of these methods and a multiple tissue block technique.

A method of examination of the heart at autopsy was developed which combined the virtues of the traditional methods with a higher degree of accuracy of heart weights. Various methods of separating the ventricles were tried until a procedure which was simple and reasonably speedy was evolved. To verify the accuracy of these results a project of micro-measurement of fibre size was embarked upon.

Thus the plan of this work was to investigate the incidence and pattern of pathological reactions in the myocardium, to establish their clinical significance and aetiology, and to determine their inter-relationships.

CHAPTER ONE

Material and Methods for Light Microscopy

HUMAN MATERIAL

The human tissue examined and reported in this study was obtained from three sources.

Routine Autopsy Series of Hearts

From February 1959 until August 1960, I performed, or was present at, two hundred and fifty post-mortem examinations carried out on adults dying in the Royal Infirmary, Dundee. Less than half (43%) of these autopsies were carried out by me, the others being conducted by my colleagues in the Department of Pathology of the University of St. Andrews. It was by their whole-hearted co-operation in this project that I was given the hearts from the subjects intact, or opened in the way detailed below.

No selection of material was made. My attendance at the autopsies carried out in the Royal Infirmary was a daily event occasionally interrupted by routine committments, attendance at meetings, and holidays. It is fair to say that these cases are a truly random sample of the subjects of post-mortem examination in this general hospital.

The hearts obtained at these two hundred and fifty autopsies were dissected, weighed, measured and examined

macroscopically by me personally. Tissue blocks were processed as detailed later in this chapter and the remaining tissue was kept in formol saline.

The blocks from only one hundred and twenty-five of these hearts have been cut, stained and examined microscopically and it is this material which constitutes the "routine autopsy series of hearts."

The order in which the paraffin blocks were taken for cutting was not necessarily numerically determined. After the tissue blocks were embedded, they were placed in a box from which the technicians removed them for cutting. Neither they nor I at this stage knew the clinical or macroscopical details of the cases from which these tissue blocks had come. For this reason, and the fact that post-mortem material from children (defined by an upper age limit of fifteen years) and fatalities after cardiac surgery was excluded, the autopsy numbers are not necessarily consecutive. No case from which blocks have been cut and stained has been excluded, and no material from "an interesting case" has been "hurried through" for inclusion, so that this series represents a truly random sample in as far

as any autopsy series is a random sample.

The histology of these hearts was carried out without knowledge of the clinical details or macroscopic descriptions. From the time that the description of the fresh heart had been noted, together with the weights and measurements, this information was not consulted until after all the sections from all the blocks of that case number had been reported. Only then were the clinical notes obtained from the central records office. An abstract of these notes was prepared, to which were then added the summary of necropsy findings and clinicopathological summary of the pathologist who performed the autopsy. This information, together with my own findings both macroscopic and microscopic, is detailed at Appendix A in Volume II.

Diphtheritic Series.

Paraffin embedded blocks of tissue from the hearts of thirteen children who died from diphtheria were kindly given to me by Professor A.C.Lendrum. The material dates from

the years 1945-1947 and was collected from different centres in Scotland. The summarised clinical histories and histological findings are given at Appendix B in Volume II.

An Example of Idiopathic Cardiomegaly

Professor H. Meessen, Director of the Institute of Pathology, Medical Academy, Düsseldorf, kindly suggested that while in his laboratories learning the technique of electron microscopy, I should examine the heart and histological material from the autopsy of a young girl in whom a diagnosis of "Idiopathic Cardiomegaly" had been made. This I did, and details of the clinical and operative and pathological findings in this girl are given at Appendix C in Volume II.

EXPERIMENTAL MATERIAL

The experimental animals used come from two sources. The experiments on rats were carried out in the Royal Infirmary, Dundee, in the Department of Pathology of the University of St. Andrews, using Hooded Lister rats from the

Rowett Institute, Bucksburn, Aberdeenshire.

The hypoxia experiment using white mice was carried out in the Institute of Pathology of the Medical Academy of Düsseldorf. The animals came from the stock of white mice reared in the Institute.

Method of Dissection of the Heart

Following the opening of the pericardium and inspection of its cavity, the parietal layer was dissected upwards until the origin of the great vessels could be identified. A finger was introduced behind the aorta and pulmonary artery and a bistoury was then inserted alongside the finger to cut the great vessels. Lifting the heart, the four pulmonary veins could be identified and cut.

Following removal from the body the heart was immersed in formol saline and usually within an hour or so, dissection was carried out.

A combination of the classical methods of opening the heart was employed.

By means of a bistoury, as in Virchow's method, the right auricle was opened from the inferior to the superior vena cava. After dissection of the appendage so that it could be laid on a flat cutting surface, the right auricular appendage was cut off two to three cms. from its ill-defined tip. A second incision in the heart was now made which joined the first incision with the line of

excision of the appendage. The right auricle was now examined and the tricuspid valve was viewed from above. The left auricle was then opened by incisions which connected the stumps of the pulmonary veins. The left auricular appendage was excised 3-4 cms. from its well-defined distal tip. The auricle, septum and superior surface of the mitral valve could now be examined. Examination by probing for an interatrial foramen was carried out at this stage.

The coronary vasculature was now dissected. It was found that whereas previous dissection of the auricular appendages aided coronary examination, if the vessels were looked at after dissection of the ventricles, the problem of following the branches was more difficult. Another advantage of following the vasculature at this stage is that any personal bias due to knowledge of the presence, and distribution of myocardial ischaemic lesions is not allowed to influence the subjective assessment of the degree of atheroma, or the amount of care with which the coronary vasculature is dissected. The coronary vasculature was examined in a routine and stand-

ard way.

The aortic stump was opened with a pair of scissors to enable the coronary ostia to be studied from the aortic luminal aspect. The left thumb was placed in the ostium of the right coronary artery and with the forefinger of the same hand the main branch could be palpated in its proximal centimeter or so. The vessel was transected with a sharp knife about 1 cm. from its origin; thereafter the vessel and its branches were cut at 3-5 mm. intervals. The left coronary ostium was similarly inspected and the main branch was transected with a sharp knife in its short course before it divided into circumflex and anterior descending branches. These branches were transected at 3-5 mm. intervals as were their branches in turn.

The dissection of the coronary vasculature is greatly facilitated by working with dry instruments, on a dry board. If the heart is gently wrapped in a dry cloth excess moisture is absorbed before the dissection is started. Scissors should never be used to open up a coronary vessel until transection has revealed the state of the lumen and wall. Blind scissor dissection can do untold damage to

coronary vasculature and, of course, can macerate thrombi. Having seen a vessel on cross section and assessed the degree of vascular thickening, endothelial thrombosis and percentage diminution of luminal diameter, the 3-5 mm. segment between cross sections may be opened with fine scissors, provided the lumen can be seen from end to end.

As a routine the diameters of the right coronary artery, the left coronary artery, the anterior descending branch of the left coronary and the left circumflex coronary artery 1 cm. from their origins, were measured. As has been mentioned, an attempt was also made to assess the degree (as a percentage) to which a vessel was left patent by the encroachment of atheromatous plaques and thrombi. When many small channels honeycombed the old thrombus, no accurate macroscopic assessment was possible and such a vessel was described as "honeycombed". Narrowed segments containing suspected thrombus, intimal haemorrhage and so on were taken for section.

The vessels examined were the left coronary artery, the anterior descending branch (and its primary rami) and the circumflex branch with its rami to the anterior wall

of the left ventricle, to the obtuse margin of the heart and to the posterior wall of the left ventricle. From the right coronary, branches to the posterior interventricular sulcus and posterior wall of the right ventricle, and acute margin of the heart were traced and examined (fig. 1.). Seldom were branches to the auricles large enough for examination.

Not infrequently calcification in atheromatous coronary vasculature makes transection in situ impossible. In such cases the coronary vasculature was dissected off the epicardial surface of the heart. Usually in these cases it was sufficient to dissect along the right and circumflex vessels and branches only as far as the right and left borders of the heart, and along 6-8 cms. of the anterior descending branch of the left coronary. Distal to these points, calcification is less common but when present the vessels are of such small calibre that accurate transection in situ is possible with little more than the normal cutting pressure. Having dissected the calcified vessels off the heart and the fat off the vessels, on a board, preferably grooved (as shown in fig. 2), the vessels can be transected by firm even cutting at right angles.

Occasionally, even with care, the vessel crumbles and no assessment of the luminal capacity can be made, but this is the exception rather than the rule. Suspect calcified segments were taken for histological processing following decalcification.

Dissection of the ventricles was now carried out (fig. 3) using a technique similar to that of Zenker as described by Roessle (1932). The first ventricular incision is at right angles to the long axis of the heart to separate the distal third of the ventricles. The atrial-ventricular valves may be inspected on their ventricular aspects and some assessment of functional abnormality may be made by palpating the two sides of these valves with thumb and forefinger. With a bistoury a cut is now made in the angle formed by the interventricular septum and anterior part of the free wall of the right ventricle, to emerge at the pulmonary valve. The valvular attachment of the anterior tricuspid papillary muscle is now divided with scissors. The second bistoury cut is along the right border of the heart and through the tricuspid valve. A similar bistoury incision along the left border of the heart opens up the mitral valve and finally an incision is made along the

junction of the interventricular septum and anterior wall of the left ventricle to emerge through the aortic valve. Care to avoid damaging the pulmonary valve must be taken with this incision. The attachment of the posterior mitral papillary muscle to the mitral valve is now divided with scissors.

The thickness of the myocardium of the right and left ventricles is measured at the base. This figure excludes the thickness of the trabeculae which may amount to about one-third of the thickness of the left ventricle and two-thirds that of the right.

The circumferences of the valves are also measured.

The heart weight at this stage is an inaccurate index of the amount of myocardium present, a large and varying proportion of this weight being accounted for by fat, coronary arteries, pieces of aorta, pulmonary artery and so on. In addition, although ventricular muscle thickness often betrays hypertrophy, and right over left, or left over right myocardial preponderance, the ratio of the relative muscle weights of the right and left sides serves as a more accurate index of these abnormalities.

It was in an attempt to overcome these difficulties

that Müller (1883), Lewis (1914) and Herrmann and Wilson (1922) stripped off non-myocardial tissue and subsequently weighed the myocardium as left and right parts.

Any such method must not be as time consuming as many of these reported methods are, and preferably should not involve the division of the septum, a manoeuvre of much subjective variation. The method finally arrived at is simple, and is a modification of that of Fulton and his colleagues (1952).

After inspection of the endocardium and pericardium the atria are separated from the ventricles by cutting round the atrio-ventricular ring with scissors.

The isolated ventricles are stripped of external fat and vessels by dissection. By cutting along the angle formed by the posterior wall of the right ventricle and the interventricular septum, the proximal two-thirds of the free wall of the right ventricle is detached. The remaining part in the excised distal third of the ventricles is freed by dividing the rest of the right ventricle from the interventricular septum. The constituent parts of the right ventricle and those of the left ventricle and septum are weighed on scales accurate to 5 G. The third weight is that of "the

rest of the heart" consisting of auricles (without appendages) and attached parts of the aorta and pulmonary artery. Occasionally the removed fat was weighed to give some figure of the degree of pathological adiposity but the technical problem of dissecting the fat from the auricles makes this a time-consuming and inaccurate assessment.

In any method of dividing the heart into right and left portions, the allocation of the septal weight has posed a problem. Müller's mathematical solution was to divide the septal weight between right and left sides in proportion to the weight of the free walls. Lewis included a slice of septum with both ventricles giving two closed cavities and a small strip of septum, which was neglected in comparing the weights of the two ventricles. By cutting along a white line in the septum, assumed by Herrmann and Wilson to form the division between left and right halves, serial horizontal sections were divided into right and left portions. Of the three methods, that of Müller is the least likely to subjective variation but even here, although the free wall of the right ventricle is well defined from the septum, the same cannot be said for that of the left side. Individual choice of the site of cutting need not be great to produce a relatively large proportional variation in weights.

Having surveyed forty-six hearts in which isolated right ventricular hypertrophy had occurred and a further forty-six hearts in which "primary left ventricular hypertrophy" occurred, Fulton and his co-workers found that the weight of the septum exceeded their accepted upper limit of normality (60 G) in only 31% of cases in the right ventricular hypertrophy group who were in failure, but in cases not in failure, the septal weight was invariably within normal limits. The increase in septal weight when present was only slight and in no case was 70 G exceeded. However, in hearts with left ventricular hypertrophy, the septum was overweight in 80% of all cases, and the increase in weight was often considerable. Fulton thus concluded that it seemed reasonable to consider the septum and left ventricle as one part of the heart and the right ventricle as the other. This argument is strengthened by the study of the "spherical dynamics" of the heart by Rodbard and his colleagues (1959). Their experimental results suggested that myocardial performance and oxygen consumption are determined primarily by the tension in the heart. If the two ventricular cavities normally eject approximately equal volumes, since the mean pressure in the right ventricle is only about

10 mm.Hg. the tension generated in this chamber is probably only about 10% of the tension in the left ventricle, which of course includes the septum.

After weighing the ventricles, the cut surfaces and endocardial aspects were closely examined with a X3 loop. Blocks were then cut from the left ventricle. From the outflow tract and upper third of the left ventricle and septum, anterior, posterior, left and right lateral vertical blocks were cut. Three transverse blocks were cut from the left ventricle and septum from anterior, and right and left posterolateral aspects of the heart and finally a vertical block through the apex was taken, giving a total of eight blocks from the left ventricle and septum. The posterior mitral papillary muscle was cut out with its ventricular base and it was through the base that the block for left ventricular micromeasurement was prepared. The papillary muscle was then cut transversely and finally split in the opposite direction to give a base block, a transverse block and two distal blocks at right angles to this. Occasionally the muscle was too thin to allow this final splitting so that either four or five blocks were usually available from the posterior papillary

musculature of the left ventricle.

On the right side the anterior tricuspid papillary muscle was cut out with its base. This base area after trimming yielded usually only one block which together with a transverse block and a distal block at right angles yielded a total of three pieces of tissue. Anterolateral and posterolateral vertical blocks were cut from the outflow tract of the right side. A posterior vertical block through the tricuspid ring and a horizontal block about half way down the ventricle on the anterolateral aspect gave a total of four blocks from the free wall of the right ventricle. Each excised piece of auricular appendage was divided into three or four pieces so that the total number of blocks from each heart amounted to about twenty-five. If, however, certain areas not included in these selected zones showed evidence of abnormality, further slices were cut, trimmed and processed. In this category were included segments of coronary vasculature in which occlusion or near occlusion was present, and abnormalities of the valves.

Methods of Fixation

".... la fixation est la pierre angulaire, la fondement de toute bonne histologie" (Langeron, 1934).

Of no tissue is this more true than the myocardium. Without doubt much of the argument about the significance of certain myocardial changes arises from the examination of material fixed in a solution which has lacked the penetrating power to inhibit enzymatic action rapidly and simultaneously throughout the tissue. Ideally the interaction of fixative with the tissue must form the same fixation compound throughout the mass and to a uniform degree. The fixative must exert a stabilising coagulating effect that will prevent immediate maceration or swelling, distortion or retraction, or the later production of these changes by the dehydrating and clearing solutions.

Formalin is an unsatisfactory fixative. Whether in water or saline, neutral or acid, it penetrates slowly (Underhill, 1932). It fails to harden the tissues quickly enough to allow easy trimming of large blocks, whereas if the desired block be cut at the beginning there is a high probability of its undergoing twisting in the fixative. This is especially true of such a tissue as myocardium, in which

muscle and connective elements are present in the same block. If any twisting occurs it is almost certain to be worsened during dehydration. Tissues fixed in formalin show a high final coefficient of shrinkage (Underhill). Formalin deposit is another factor which condemns this substance as a fixative for post-mortem material.

Formol sublimate (90 ml. of saturated aqueous corrosive sublimate with 10 ml. of commercial formalin) is a stable mixture which combines the coagulant virtue of a corrosive with the antilytic action of formalin (Lendrum, 1941). Coagulation is rapid and after some four or five hours in this mixture, it is possible to select particular areas and trim blocks from the larger portions of tissue taken at autopsy. The degree of fixation already achieved means that the faces thus chosen will remain more or less undistorted during further fixation. In post-mortem material, this solution does not completely inhibit lysis so that for other than biopsy material, an initial hour or so in 5-10% formalin in normal saline, fixes the blood. This is followed by formol sublimate to exert its coagulating effect and after some 12-18 hours

the tissue is transferred to saturated aqueous corrosive sublimate. This secondary use of saturated sublimate does not have the hardening effect seen when it is used as a primary fixative. The tissue may be left in the saturated sublimate for up to three months without showing obvious deterioration, and indeed it is generally better to allow tissue to be acted upon by the saturated corrosive for at least six weeks.

There is no ideal fixative. However, it is considered that the formol saline, formol corrosive followed by saturated corrosive sequence is the best series of fixative solutions at present available for the human myocardium obtained post-mortem.

However, what gives excellent results as a fixative for human material, does not necessarily produce correspondingly satisfactory results in animal tissue. Considerable difficulty was encountered in attempting to fix rat tissue satisfactorily, the sequence used for human material giving too hard a block.

Bouin's solution has been found to be too acid for human post-mortem material. Even when the content of

acetic acid is much reduced, blood is lysed and connective tissue assumes a swollen, gelatinous form. Tarkhan (1931) showed that picric acid itself produces swelling and dissociation of ligament and tendon. It was shown to have a poor penetrating power (Underhill) and attempts which were made to remedy this (for example, by adding such compounds as urea) met with little success. However, in spite of this, although far from ideal, Bouin's solution has been found to be the most satisfactory of the fixatives sampled for tissue taken from the rat.

Dehydration of the Fixed Tissue

After dehydration by the normal routine methods, myocardium, especially if fibrosed, is difficult to cut. Substitutes for ethyl alcohol and chloroform have been extensively investigated by Lendrum (1941). Aniline (Painter, 1924), cinnamic aldehyde (McClung, 1937), graded cellosolve dilutions, tertiary butyl alcohol (Johansen, 1935), iso-butyl alcohol (Hewitt, 1931), methylal (Dufrenoy, 1935), Lang's N-butyl alcohol series (1937), and most satisfactory of all according to Lendrum, the butyl alcohol series of Stiles (1934) were assessed. Butanol

is a clear liquid which dissolves only one-twelfth its weight of water but is freely miscible with ethyl alcohol and allows the preparation of a series of solutions in which tissues can be brought gradually to absolute butanol without undergoing the denaturing action of absolute ethanol. From butanol, tissue can be transferred directly to paraffin. However, a further step has been found to be profitable with such traditionally "difficult" tissue as myocardium. From butanol, the blocks were placed in equal parts of butanol and aniline plus 10% acetone. This solution was changed once and the tissue was left in it for anything up to three months.

One of the outstanding conveniences of the butyl aniline series is the fact that tissue can be left for days in any of the solutions without coming to any harm. The general routine followed was to move the tissues once a day on a hand operated histokine.

The cutting of dense tissues, such as myocardium, is greatly facilitated by a combination of butyl-aniline dehydration with double embedding on the principle of Peterfi (Romeis, 1932). The Peterfi method utilises

a dilute solution of pyroxylin (celloidin) in methyl benzoate to give the tissues, after dehydration and before clearing for paraffin, a thin infiltration with nitrocellulose. The schedule thus is completed after immersion in the aniline-acetone mixture by giving the tissue two changes of methyl benzoate followed by a 2% pyroxylin mixture in methyl benzoate. The tissue is left in each of these last three solutions for 24 hours (although it may be left in the celloidin mixture for up to a fortnight). After this impregnation the blocks of tissue are placed in one of the paraffin solvents, of which benzene has been found to be satisfactory. After two changes of benzene (half an hour each) the tissue is put into melted paraffin wax at 60°C for 24 hours. The paraffin wax is changed three times during the 24 hours and after two changes the tissue is impregnated with the help of a vacuum oven (Lendrum, 1941).

Methods of Staining

Initially six sections were cut from each block at a thickness of 6-7 μ.

The first section was stained with Mayer's haemalum

and 1% eosin.

The second was stained overnight with Lawson's modification (1936) of the Weigert-Sheridan elastica solution followed by solochrome prune and haemalum nuclear staining. Solochrome prune S.A. is a commercial dye which is used in place of celestin blue, the working solutions of these two dyes being prepared in the way suggested by Lendrum (1951). This was followed by treating the section with a saturated solution of picric acid in 80% alcohol to which had been added 0.2% Orange G. This modification has been found to differentiate the nuclei and stain the erythrocytes bright yellow; in addition, background staining is cleared and the subsequent staining is improved. After a wash in water the section was then stained with Lendrum's (1951) modification of van Gieson's solution for 5 minutes, rinsed in methylated spirit, dehydrated in absolute industrial alcohol, and cleared in xylol.

Silver impregnation of the reticulin of the third section was carried out by the method of Slidders, Fraser and Lendrum (1958). This was found to give consistent results and a clear pattern for the study of reticulin

abnormalities and the measurement of cardiac fibre thickness at the base of selected papillary muscles. These reticulin preparations were counter-stained with Scarba red (Slidders et al. 1958).

Eosin is a poor cytoplasmic stain for myocardial tissue. Even when well differentiated, a section counter-stained with eosin gives an inadequate resolution of the myofibrillar arrangement and consequently an attempt was made to develop an adequate staining method for its demonstration. Variations of eosinophilia may be of dubious significance if the myofibrils cannot be adequately seen.

It was hoped to develop a simple and suitable staining method which would not only give a sharp differentiation between collagenous and muscular tissues but also a detailed myofibrillar pattern showing the bands and discs of the myocardium. Trichrome methods based on Mallory's use of phosphotungstic and phosphomolybdic acid were investigated. By the original Mallory method the "endoplasm" is stained red and the "exoplasm" blue. Erythrocytes appear orange coloured and fibrin is stained red. The aim for myocardial structural study was to produce a yellow

coloured "exoplasm" so that the endoplasm, particularly the myoid substance, would be more clearly seen. The first method tried was a modification of the Masson procedure, called by Lendrum (1957), the Fast Red Masson method. Following nuclear staining with solochrome prune and Mayer's haemalum, the section is immersed in kiton fast red (Ciba) 1% in 1% aqueous acetic acid for five minutes. After a rinse in water, fix in 1% aqueous phosphomolybdic acid, for five to ten minutes, rinse and stain with lissamine yellow 2 G (I.C.I.) 1%, tartrazine 1% in 1% aqueous acetic acid for two to three minutes. Rinse in 95% ethanol, absolute ethanol and so to xylene. This method, although of use for a good low-power trichrome photograph, was found to reveal little of the finer myocardial histological detail.

The second method employs "a novel principle, which combines something of the Masson technique, the use of stilbene yellow along with the red acid wool dye as suggested by Emig, and a Lucky thought to establish these dyes in their place by after-treatment with phosphomolybdic acid. For convenience this new method is called the MEL method" (Lendrum, 1957). The nuclei are stained as described

above. Following a wash in water, staining is carried out in a freshly prepared mixture of two parts 1% Azogeranine 2 G (I.C.I.) in 1% acetic acid, to four parts 0.5% direct yellow (Old C.I. 620), in 1% acetic acid for five minutes. Rinse briefly in water and fix in 1% aqueous phosphomolybdic acid for ten to thirty minutes. Rinse in 95% ethanol, absolute ethanol and so to xylene. This staining mixture was not found to give adequate differentiation of the myoid substance, and in an attempt to promote redness, stronger red dyes were tried among which was 1% chromozone. The yellow dye was also varied and the best combination was a chromozone-poly yellow mixture, "poly yellow" being one of the stilbene yellows, polyphenyl yellow 83 (Geigy). The proportion of red to yellow dye was varied and in addition, the phosphomolybdic acid was replaced by phosphotungstic acid, which had the advantage that it prevented the yellow stained areas from taking on a greenish tinge after a few weeks.

Combinations of the Fast Red Masson technique and the MEL technique were possible but once again differentiation was inadequate. Of the acid red dyes phloxin produced the most consistent results. Numerous yellow dyes were tried.

Of Lissamine flavine FSS, polyphenyl yellow 8 G, Naph. Leather yellow 5 GN (AY85B), Coomassie fast yellow GS (AY85), Durazol yellow 4 GS (DUY44), Durazol yellow 6 GS (DY46) and Milling Yellow 3 G (Yorkshire Dye Ware Company), the last was found to give the best results. The phloxin-milling yellow sequence gave reasonable results but differentiation was occasionally patchy and not infrequently difficult to control. By chance Professor A.C.Lendrum discovered that if a section was left exposed to a degreasing agent such as xylol for a day or so before staining, differentiation of the Masson type is much more even and occurs more gradually. The differential dye affinities appear to be more accentuated and the curve down which differentiation proceeds is straightened, reduced in steepness and increased in length.

Of the degreasing agents tried (xylol, pink paraffin, blue paraffin, carbon tetrachloride and trichlorethylene) trichlorethylene was found to facilitate differentiation satisfactorily and in particular to ensure the production of yellow erythrocytes before differentiation was complete in the myocardium.

Degreasing is carried out on sections before staining.

After a rinse in xylol, the section is rinsed in cellosolve and placed in a jar of trichlorethylene. For myofibrillar staining the section should be left in this solvent for at least forty-eight hours and preferably double that time.

After a rinse in cellosolve and water, Mayer's haemalum (one to two minutes), Scott's tap water substitute (two minutes) and phloxin (thirty minutes) were followed by a cellosolve rinse, then a trichlorethylene rinse and trichlorethylene overnight before differentiation in a 2.5% solution of Milling Yellow in cellosolve. The speed of differentiation varies with the number of times the Milling Yellow solution has been used and careful microscopic control of differentiation is essential to begin with until some idea of the speed of action of the solution is gained.

Experience with these various methods resulted in the conclusion that the advantages of regressive methods depending on differentiation in which the subjective factor was introduced into the result, far outweighed their inherent disadvantages. In myocardium, differentiation can be allowed to proceed as far as is demanded by the degree of

abnormality of the pattern. Normal myocardium will need little differentiation. Soon, the myofibrillar pattern (figs. 4 and 10), bands and discs (figs. 5 and 7) will be seen holding on to the phloxin following its replacement by the yellow dye in collagen and erythrocytes. However, if a zone of necrosis is present, it is possible to allow differentiation to proceed until only the abnormal muscle is holding on to the red dye (fig. 9). Fine detail of normal and degenerating myocardium is readily seen by this method of staining. After differentiation, the sections are well rinsed in cellosolve, cleared in xylol and mounted in DPX.

The intercalated discs are well shown and it is of interest to note that there not infrequently appears to be distraction of the constituent halves of the disc (fig. 6), an appearance reminiscent of "Dehiszenz Glanzstreifen" reported at sub-microscopic level by Poche (1958). These light microscopy changes are an expression of segmentation at a stage which may not be seen in the routine haemalum and eosin stained section.

Early myofibrillar changes are demonstrable by this phloxin-milling yellow method of staining when combined

with degreasing techniques. Within hours of severe myocardial hypoxia there is sufficient myofibrillar derangement to produce an abnormal pattern on staining these elements preferentially. A dubious fuzzy eosinophilia is a poor substitute for a clear myofibrillar pattern. Differentiation can be allowed to proceed in the abnormal myocardium until only the coagulated protein is holding the phloxin. This abnormal pattern and subsequent lysis can be seen well and followed by this method (figs. 11 to 16). After acute infarction, by about the fourth day, this abnormal proteinous material in the necrotic muscle has been lysed or phagocytosed and the defibrillated cell is stained uniformly yellow (fig. 164.)

Fibrin is stained a brilliant red with phloxin and its resistance to differentiation is even greater than that of degenerating muscle (fig. 18). Endocardial and intravascular thrombosis is thus easily confirmed by this staining method.

The granules of mast cells are also stained by phloxin and resist differentiation in Milling Yellow.

Methods of Micromeasurement

To carry out micromeasurement on cardiac fibres it is essential that there should not be indiscriminate sampling of the right and left ventricular myocardium. Fixed points at which measurements could be made in both the right and left ventricles were selected in the hope that the figures obtained could be related to ventricular weights and nuclear densities. It was decided that these fixed points should be at the base of the anterior tricuspid and that of the posterior mitral papillary muscles. In addition, it was felt that the papillary musculature by its function and anatomical site provided an accurate and sensitive index of myocardial abnormality generally.

Sections from blocks from the fixed points selected in each ventricle were impregnated by the silver method of Slidders et al. (1958). The sections were viewed on a microscope to which the "Drawing Apparatus" of Zeiss was attached (fig. 79). This is a device by which the light from the eyepiece is reflected by a 90° prism into a lateral tube where it traverses a rotatable polarising filter I. The polarised light is then deflected upwards by a beam splitter. After having passed a fixed polarising

filter II, the light reaches the observer's eye. The light coming from the drawing area (lying on the table top alongside the microscope) enters a rotatable polarising filter III, then passes through the beam splitter and fixed polarising filter II whence it reaches the eye of the observer. The observer sees two superimposed images. The brightness of the microscope image may be varied by rotating the filter I and the brightness of the image on the drawing area by turning filter III until an illumination of the partial images has been arrived at which is most satisfactory for drawing purposes.

Using a high quality paper and a sharp pencil or fine pen, the outline of the reticulin pattern was easily followed and cross sectional distances could be drawn in, in relation to the site of the muscle nuclei. Occasionally where regular fibres were seen, the boundaries of non-nucleated fibres were outlined, but nuclear sites gave the more constant measurements. These drawings were made at a magnification of X510, and between two and three hundred fibres were measured in each section. With a pair of dividers the individual breadths of the fibres could be marked off along a line and the sum of the thicknesses of ten

fibres (i.e. at X510 magnification) was measured in millimetres and represented one unit of fibre thickness for that section. The twenty to thirty combined thicknesses of ten fibres in millimetres were added and averaged to give a final figure for the "ten fibre thickness" of the section. To convert a ten-fibre-thickness to an absolute individual fibre thickness, the formula is:

$$a = \frac{U}{M \times 10} \text{ mm.}$$

$$= \frac{100\ U}{M} \mu.$$

where:

a = Absolute fibre thickness

U = "Ten fibre thickness" (units)

M = Magnification.

Methods for Electron Microscopy

Mature white mice from the animal house of the Institute of Pathology, Medical Academy of Düsseldorf were used in Experiment H. The still beating heart was excised and immersed in a large drop of 1% osmium tetroxide solution on a piece of cardboard. With two clean safety razor blades cutting in parallel but different directions, the heart was cut into three pieces. The middle third was then cut into approximately 1 mm. cubes in the osmium solution and the other two thirds were processed for light microscopy.

The small cubes of tissue were transferred from the osmium solution on the piece of cardboard to fresh 1% osmium tetroxide in small test tubes which were left at 0° - 4°C for one hour. At this temperature, autolysis is to a large extent inhibited while the osmium solution diffuses through the tissue to bring about fixation.

Two methods of preparing the 1% osmium tetroxide were employed, half the material being fixed in the solution described by Palade (1952) and the other half in Sjostrand's solution. Both are 1% osmium tetroxide

solutions buffered with veronal but whereas Palade's solution is hypotonic Sjostrand's solution is isotonic. After an hour in an osmium solution the small cubes of tissue were rolled in a tube of cotton bandage, the ends of which were closed by thread, and suspended in distilled water in the Bernhard (1955) apparatus (fig. 80). If methycryate is to be used for embedding, the main bulb of the apparatus is filled with absolute alcohol and slowly run into the reservoir in which the tissue is suspended. Dehydration by this means is carried out for an hour before the small cubes of tissue are transferred to a test tube containing absolute alcohol. Three changes of alcohol were then used in the next half hour following which the tissue was transferred to a mixture of equal parts of methacrylate and absolute alcohol for ten minutes. The tissue was then left overnight in a methacrylate mixture without the addition of the polymerising activator and next day transferred to a methacrylate mixture (to which 0.5% activator had been added) for fifteen minutes, after which five changes of the solution were carried out at quarter-hour intervals.

The "methacrylate" consists of a mixture of methyl and butyl methacrylate in the proportion which yields the

degree of hardness of block which is required for ease of cutting the particular tissue used. For myocardium, the mixture recommended and used was three parts methyl to seven parts butyl methacrylate.

Embedding was carried out by heating the methacrylate mixture to 90°C until it had the consistency of honey. This sticky fluid was then poured into small gelatin capsules, a piece of tissue then being gently probed into the bottom of each capsule, which was covered with a gelatin cap. The filled capsule was placed in an oven at 60°C for forty-eight hours following which the gelatin was peeled off. The methacrylate block was trimmed and ready for cutting.

An alternative embedding medium is Vestopal W (Ryter and Kellenberger, 1958). Although the contrast obtained for photography is not so good with Vestopal as with methacrylate, the ease of cutting produces a flatter and more consistent field with less cutting defects. As a beginner, I found much less difficulty with the embedding and cutting of material in Vestopal than in methacrylate. The illustrations used in this thesis have been prepared from Vestopal embedded material. Before embedding in Vestopal

dehydration is carried out in the Bernhard Apparatus using acetone for one hour. The pieces of tissue were then transferred to fresh acetone in small test tubes. The acetone was changed every half hour, six times, after which the tissue was dropped into a mixture of one part Vestopal to three parts acetone for half an hour. This was followed by half an hour in a mixture of equal parts acetone and Vestopal followed by immersion overnight in a mixture of three parts Vestopal to one part acetone. Finally the tissue cubes were placed in a mixture of Vestopal W to which was added initiator (1%) and activator (0.5%), for half an hour, following which the tissue was embedded in gelatin capsules which were filled with this mixture. The capsules were placed in an oven at 60°C for twelve to forty-eight hours. Polymerisation of the plastic caused hardening, following which the capsule could be stripped off and the block was ready for trimming and cutting.

The Porter-Blum ultramicrotome was used with glass knives for cutting sections the thickness of which was judged by their colour as they floated off the knife in acetone-water. A silver grey coloured section is said

to measure about 500 Å, and this was the thickness aimed at. The sections were mounted on copper grids coated with a formvar film (Reimer, 1959) and were then ready for use in the microscope.

The R.C.A. Electron Microscope EMU-3 was used and all microphotographs were taken at an accelerating negative voltage of 50 KV. The magnifications used usually ranged from 5,000 to 15,000 diameters, a four or five-fold further increase in magnification being attained photographically. Photographs were taken on a strip of fine grain plate on which there were five exposure areas each of 4 cm. square.

CHAPTER TWO

The Structure of the Myocardium

In this study of the reaction of the myocardium, an attempt has been made not merely to look at the fibres, but to look into them. The normal arrangement of the myofibrils, the range of nuclear appearances and the relation of the intercalated discs to the cells, were problems which light microscopy had failed to resolve adequately; thus to establish a range of normality, the results of ultra-structural research on the myocardium were surveyed.

During a two-month stay in Düsseldorf I studied the techniques of the preparation of tissues for electron microscopy (pages 35-39) and learned the theory and technique of using the R.C.A. Electron Microscope EMU-3. In addition to looking at the myocardium of experimental animals in which starvation, specific deficiencies or intoxications had been induced, or on which surgical operations had been carried out by members of the research staff, I carried out Experiment H for which the processing, cutting and photography were completed by me. It is the control material from this experiment with which this chapter on the electron microscopic structure of the normal myocardium is illustrated.

The syncytial nature of the myocardium and the intercalated discs have been considered to be the features which typify the muscle of the heart. The syncytial myth provided an obvious anatomical basis for the explanation of the fact that conduction, which remains restricted to the stimulated fibre in skeletal muscle, passes from fibre to fibre in cardiac muscle.

The role of the intercalated disc has provided fertile ground for speculation. The discs have been interpreted as sites of formation of new sarcomeres (Heidenhain, 1901) as devices for co-ordination of the contraction of the myofibrils (Dietrich, 1910) or as irreversible contraction bands (Jordan H.E., 1911 and 1912).

Some investigators questioned the syncytial nature of myocardium and regarded the intercalated discs as accumulations of intercellular cement lines (Schweigger-Seidel, 1871, and von Palczewska, 1910) or tendinous junctions between individual cells (Marceau, 1904).

Using an electron microscope nearly fifty years later van Breemen (1953) came to the same conclusion. Any remaining doubts of the cellular nature of the myocardium were

dispelled but because of technical problems which the last few years have helped to solve, an insufficiently high degree of resolution led van Breemen to consider that the intercalated discs were extracellular and represented "collagenous invasion at cell wall junctions". The electron microscope has since revealed that the intercalated disc is formed by three components, the opaque osmiophilic layer of the sarcolemma bounding the cell terminally, an interspace 150-200 Å wide, and the corresponding segment of the inner layer of sarcolemma of the adjacent cell (compare fig. 82 with fig. 81). Most of the material responsible for the appearance of the intercalated discs on light microscopy consists of a zone of dense cytoplasm located at the cell boundary. These observations were made in a preliminary report by Sjostrand (1954) in Copenhagen, and independently by Poche and Lindner (1955) in Düsseldorf. Following the publication of these papers the findings have been confirmed by electron microscopists in many centres. The final results of the detailed study of the ultra-structural organisation of the intercalated discs and their subdivision into regions of different structural arrangements were published by Sjostrand and his colleagues

in 1958.

The intercalated disc is formed by the plasma membranes of the adjacent cells and a space between the two. By light microscopy, intercalated discs have not been demonstrated in embryonic or early foetal life (Witte, 1919), and it was thought that they increased in number and complexity with age (Jordan and Steele, 1912). Investigations carried out with the aid of the electron microscope by Muir (1957) disproved many of Jordan's conclusions. Embryonic cardiac muscle is not syncytial, intercalated discs appear early in pre-natal life, myofibrils never cross discs without apparent interruption, and it is not true to say that the number of discs increases with age. The dense material on the cell membrane occurs only at points where the membranes transect a myofibril and as the membranes occasionally run for long distances between and parallel to myofibrils it only appears that discs are superimposed on a nucleus, or incomplete or interrupted in their course across the fibre. This is explained by the unresolvability of the cell membranes by light microscopy. It was considered by Jordan (1911) that the area bounded by adjacent discs might contain more than one

nucleus. That adult cardiac muscle cell may be multinucleate is entirely probable as Werner (1910) stated that each "muskelterritorium" contained two to thirty-two nuclei, the usual number being eight. Muir's observations that early embryonic muscle is mononucleate and that mitoses can be observed after differentiation of myofibrils, lends support to the suggestion that the multinucleate state of the adult myocardium is produced by nuclear division without cytoplasmic separation. The principal conclusion from Muir's study is "Cardiac muscle is cellular throughout its development and in the adult, and there is no valid evidence to contest the statement that the intercalated discs are specialised regions of cellular adhesion."

The myocardial cell is surrounded by a dense protomembrane or plasma membrane (figs. 82 and 83). There is another membrane, the perimembrane, lying outside the protomembrane. This is less opaque than the plasma membrane and separated again by an interspace of further decreased opacity. The perimembrane stretches undisturbed over many cells. In some species (e.g. mouse) it is not as easily seen as in others. Nevertheless in figs. 82 and 83 some

segments of the sarcolemma show their constituent membrane layers.

There is considerable confusion of terms in the literature of cell membranes of the myocardium. The term sarcolemma to Perry (1956) means the peri and protomembranes together, but to Barer (1948) the protomembrane only. Lindner (1955) calls this combination of proto and perimembranes the "exomembrane". In this study Perry's concept of the term is used.

What is called the myofibril is part of a synfibrillar system irregularly split into branches composed of 200-1000 myofilaments (figs. 82 and 83). Fibril diameters vary from about 0.5 to 2.0 μ as observed in longitudinal and cross sections. This unbound arrangement of filaments means that they are directly bathed by sarcoplasm and any change in the medium will directly affect the bundles. All classical bands of skeletal muscle are visible in heart muscle in the range of its state of contraction. In fig. 84 is shown a diagrammatic representation of the band patterns of the myocardium and skeletal muscles.

The myofibrils are inserted by a cement substance (Poche

and Lindner, 1955) into the lamina of the intercalated discs at each end of the cell. The cement substance is similar in appearance to Z line substance.

Possibly the most striking feature of myocardial histology is the number of mitochondria to be seen lying between the fibrils (figs. 82, 83, 85 and 86) without apparent respect to the sarcomeres. They measure from 0.3 to 1.7 μ in length and from 0.2 to 1.0 μ in width. A double outer membrane is regularly visible if the mitochondrion is cut at right angles (fig. 86), and at right angles to this are a series of inner double membranes or cristae.

The mitochondrion is a particulate structure which catalyses the oxidation of pyruvic acid to carbon dioxide and water by way of the citric acid cycle, and couples these oxidations to the synthesis of adenosine triphosphate from adenosine diphosphate and inorganic phosphate (Green, 1959). The mitochondrion is thus an energy producer. However, there are some variations on this particular metabolic theme, as not only pyruvic acid, but other compounds capable of transformation to pyruvic acid or its products, can feed into the citric acid cycle in different types of mitochondria.

Aminoacids and fatty acids fall into this category. However, basically, mitochondria allow the coupling of citric cycle oxidations to esterification of inorganic phosphate.

It has been estimated that each mitochondrion requires twenty to forty different proteins and about a dozen co-enzymes to carry out its enzymatic roles. The mitochondrion is of a size sufficient to accommodate several hundreds of each of the component proteins. Thus as Green points out it is unlikely that the whole mitochondrion is the smallest common denominator of enzymatic activity. Indeed he has demonstrated that the mitochondrion can be fragmented into progressively smaller particles which can retain all their enzymatic properties as well as the basic morphological pattern of the parent mitochondrion. Of immense interest are the results of isolating and damaging mitochondria. Electron microscopy of beef heart mitochondria, functionally examined after varying degrees of inflicted damage, revealed that when a mitochondrion loses its limiting or external membrane, the capacity for carrying out the complete citric acid cycle is lost. But as long as the double membrane structure is preserved with or without a limiting external membrane, then the capacity for

oxidative phosphorylation is preserved. When both the limiting external membrane and double membrane are lost then only the capacity for electron transport survives. Thus there is a morphological basis for the suggestior that graded functional loss parallels graded inflicted injury.

The Golgi apparatus is a small and unimpressive feature of myocardial cells.

Investigation into the fine structure of animal cells has provided evidence of the existence of a finely vacuolar system, in the cytoplasm. With the exception of the mature erythrocyte, all animal cells so far examined have revealed the presence of this vacuolar system. The reticular character of the system and its exclusion from the thin cortical layer of the cytoplasm account for the name ascribed to it, endoplasmic reticulum. In some cells this system is abundantly represented but in others it is sparse. Its form, volume and distribution tend to be characteristic for the cells of a particular type so that in effect, it is a feature of cellular differentiation. In cardiac muscle the interfibrillar sarcoplasm is usually confined to narrow

spaces which are marked by rows of profiles seemingly representative of sections of small vesicles or slender tubules (figs. 82, 83, 85 and 86). These profiles range in shape from circular to oval, to long ellipsoids, and in their smallest dimension, represent the space between adjacent myofibrils. They may be as little as 200 Å across. Within the limits of the A band the distribution of these profiles is quite uniform with greatest constancy of occurrence opposite the I band. When a mitochondrion is present in the interfibrillar space, such small profiles are found on one or both sides of it. It has been suggested (Lindner, 1955) that in fact the endoplasmic reticulum is arranged in two systems. The transverse system is said to consist of invaginations of the sarcolemma and runs in the region of the Zlines among the myofibrils. This of course will consist of the two membranes constituting the sarcolemma and in cross section it will be seen that the inner membrane is now the perimembrane. The longitudinal system consists of protomembranous invaginations running along the length of the cell in tubules one membrane thick. It is likely that there is

continuity albeit intermittent, between the two systems and it may be that there is resultant continuity between these two systems and the space bounded by the nuclear membrane. The acceptance of this transverse and longitudinal arrangement of the system of tubules is by no means universal, but even from the schematic drawings of the paper of Porter and Palade (1957), who are mildly sceptical on this point, the two constituents of this system appear to be a distinct possibility.

Some functional relationship must exist between this reticulum and the myofibrils. However, what is thought to be the function of this reticulum is largely speculative and is influenced by the known requirements of the myofibrils for metabolites and appropriate excitation. The reticulum may be regarded as a kind of intra-cellular circulatory system, transporting materials to and from the functional myofibrils. Secondly, Porter and Palade point out that the limiting membrane of the reticulum may serve as an intra-cellular conductor, "... the content of the reticulum might be kept similar to the extracellular environment by a brigade of pinocytic vesicles working across the peripheral or outer layer of cytoplasm. From this it would follow that the membrane limiting the reticulum

separates cytoplasmic matrix from a mixture and concentration of ions comparable to that of the external environment. In this role, then, it would resemble the plasma membrane limiting the cell and might be regarded as having similar structural and permeability properties. If now membrane potentials are maintained across the plasma membrane by selective membrane permeability or some other mechanism energized by metabolism within the cytoplasmic matrix, it is not unreasonable to assume that in a similar manner potentials are maintained across the membrane-limiting elements of the reticulum. Under this concept a wave of depolarisation of the sarcolemma might be picked up by or transmitted to the sarcoplasmic reticulum and thence spread rapidly as an action potential along its limiting membrane to all parts of the sarcomere. Presumably lateral conduction would be along that part of the reticulum opposite the H band, thence along the longitudinal elements, where these are present, to the discontinuities in the triads opposite the I or Z bands."

This a most attractive theory. One most interesting point is worth emphasis. The "syncytial theory" is dead but it will be noted that the individual cells are found

in chains bounded by a continuous perimembrane and indeed the space between the peri- and protomembrane is continuous throughout the myocardium (fig. 81). It may be that this is ultimately the feature which determines the ability of the myocardium to contract and relax in the unique way in which it functions and it would appear that the physiological properties of cardiac muscle are now beginning to find expression in structural terms.

CHAPTER THREE

Cardiac Growth and Enlargement

For over a century opinion has been divided on the question of the mechanism of normal growth of the heart and its enlargement beyond the limit of normality.

In 1853 Hepp propounded the theory that post-natal cardiac growth was brought about by hypertrophy. Before that cardiomegaly and normal post-natal growth were thought to result from hyperplasia, or hyperplasia with some hypertrophy. Zielonko (1875) was by no means satisfied with Hepp's abandonment of a hyperplastic element in the production of cardiomegaly, and on the basis of experiments with frogs and rabbits, and from a study of human hearts, he concluded that hypertrophy itself could not provide the entire explanation for cardiomegaly.

Goldenberg (1886), on the other hand, concluded from his studies that hypertrophy was largely responsible for normal heart growth as well as for cardiomegaly, and in 1889 Tangl, having experimentally produced aortic stenosis in rabbits, decided that hypertrophy alone was the mechanism responsible for cardiomegaly and normal growth. Wideroe (1911) chose the middle way and concluded that

the heart of man enlarges by hypertrophy and hyperplasia.

Conclusive evidence was not put forward by the champion of any of these theories until A.J.Linzbach (1947) working in Berlin, studied a series of hearts of differing weights and suggested that the myocardium is capable of hypertrophy to a "critical heart weight" of about 500 G, after which an increase in size is brought about by the splitting of fibres, in effect, hyperplasia.

Assuming the origin of the myocardium from a single cell, the cardiac fibres in normal development have been calculated to pass through approximately thirty-five generations (Black-Schaffer and Turner, 1958), the last division, believed by some to be amitotic, occurring some time between birth and three months of age. All normal human hearts must therefore have essentially the same number of cells.

Thus it is possible by micromeasurement of cardiac fibre thickness to relate fibre thickness to the heart weight. If hypertrophy is the mechanism of cardiomegaly the fibre thickness will increase with the weight of the myocardium, whereas if hyperplasia occurs, the fibre thickness will vary little. Most of the work on this problem

has been done using this basic theory but where Linzbach triumphed over most of the other workers in this field was in the care with which he selected his material for study, and the extreme accuracy he achieved by attention to his technique of preparing the material for measurement.

Material for a study of this problem can be selected from hearts of patients of differing age groups on the basis of their normality and their obvious enlargment. However, in any series of autopsies the assessment of normality of heart size is beset with difficulties. The thickness of the ventricular walls at fixed points and the weight of the whole heart are the classical measurements recorded in most autopsy protocols. Their inaccuracies are enormous. By weighing the ventricles separately after removal of fat, coronary arteries, auricles and the origins of the great vessels, and assessing the fibre size at fixed points within these ventricles it was hoped that the more accurate results would lead to a better understanding of the true heart size.

Results of Micromeasurement of the Routine Autopsy Series

From a survey of the ventricular weights, case notes and macroscopic descriptions of the hearts of this routine autopsy series of hearts, the figures for the upper limit of normality of right and left ventricles were set at 69 G and 189 G respectively. Hearts of ventricular weights above these figures were placed in one or both of two categories, "L.V. hypertrophy" group (table I) and "R.V. hypertrophy" group (table II). With normal coronary vasculature and no evidence of myocardial disease, hearts in which the ventricular weights were less than 189 G and 69 G were placed in the "normal" group (table III). In fact some of these were later found to contain foci of inflammatory disease.

The weights and measurements of the left and right sides of the hearts were carried out as detailed on pages 13, 32-34. The weights of the right and left ventricles of the three groups of hearts are shown in figs. 87 to 89, and in relation to the fibre size, cases were grouped in blocks to show fibre size in relation to the ventricular weights (figs. 90 and 91). These figures are also seen in figs. 92-95 where on logarithmic paper, the fibre thicknesses

are plotted against the ventricular weights of the three groups of hearts. Logarithmic paper has been used to draw in the small number of observations at the upper end of the groups in which the scatter is arithmetically wide, and to obtain a more regular graph curve.

These results have been summarised in figs. 96 and 97 and where the median values of each group of cases within 20 G. ventricular weight have been plotted against the weights. From these groups it will be seen that there is an expected rise of fibre size with the rise in ventricular weight. In the right ventricle, the fibre size drops at about 110 G. whereas in the left ventricle a levelling off occurs at about 220 G., with a further jump at 260 G. and a fall off at 280 G.

There is no statistical significance to be attached to the fall off in ventricular fibre size by comparison with the individual ventricular weights. There are too few observations in this upper range to be sure of the tendency for the fibre size to level off or fall with an increase in ventricular weight. All that can be said is that the graphs show a tendency to level off or fall, this

tendency being in support of the concept of each ventricle having a critical weight, after the attainment of which an increase in the number of fibres is brought about.

Another factor which undermines the establishment of statistical significance of these results is the very interesting fact that about the "critical weight" of a ventricle, the variation in size of the fibres increases. The appearances and measurements suggest that the ventricular cardiomegaly is due to the presence of two distinct fibre populations, those in which splitting has not occurred, and those in which it has. Once the critical ventricular weight is passed, this variation of fibre size is very much less, the inference being that splitting has occurred in a set number of fibres and has been followed by a redistribution of fibre size so that the average is reduced but the variation is not great.

Age and Sex

The relation of sex and age to the ventricular weights and fibre thickness is shown in figs. 98 and 99. Heart weights and measures have been grouped by decades of

patients' ages. The graphs are arithmetical in scale but logarithmic functions of the weights and fibre sizes have been used.

Women have smaller left ventricular weights than men. This is usually so for the right ventricle but in the younger decades the lines cross. It must be re-emphasised that in older obese patients, more commonly therefore in women than men, right ventricular adiposity will result in a right ventricular weight which is far from an accurate assessment.

Fibre thickness in the left and right ventricles can be seen to differ in males and females in much the same way as do ventricular weights.

From these figures the variance between the sexes and that between the age groups can be assessed (table IV), the variance being the product of the square of the deviation and the number in the group.

Clinical Sub-groups

The cases were regrouped according to various clinical

findings in an attempt to demonstrate statistically the significance of variations of overall mean ventricular weight and fibre size. Cases were arranged in numerous clinical sub-groups and as can be seen from table IV, figures emerged which were less than the standard error which is a function derived by dividing the standard deviation by the square root of the number in the group.

Thus in the hypertensive group the fibre size is significantly raised in the left ventricle, the weight of which is also of course significantly raised, although to a less significant extent.

The valvular disease group has been counted together, the fibre size and weights for both sides of the heart all being significantly raised.

In emphysema the rise in right ventricular weight and fibre size is considerable.

The myocarditis group was interesting in that no significant variation was seen apart from a borderline drop in right ventricular fibre size. The exudate and congestion can not have been a "significant" complication to the relative weights and measurements, and these cases were

left in the so-called "normal" group. In cases of cancer the tendency for a fall off in weight was seen in the left ventricle.

Discussion

The figures for the upper limit of normality are of more convenience than accuracy. There will be as many hearts in which a left ventricular+septal weight of 220 G will be normal as there are those in which a left ventricular+septal weight of 170 G will be indicative of ventricular enlargement. A second accurate measurement would be preferable before a final decision can be made on this upper limit of normality figure. The figure for the surface area of the heart would probably in relation to the weight of the ventricle give a more accurate estimation of normality.

The "R.V. hypertrophy" group was selected solely on the basis of the weight of the free wall of the right ventricle. This figure is less accurate than that of the left ventricle. Careful dissection and a constant technique are essential as it must be borne

in mind that the weight of the right ventricle is subject to not inconsiderable subjective variation. By varying the proximity to the septum of the anterior and posterior incisions in the dissection of the free wall of the right ventricle, inaccuracies of up to 15% can occur. Another problem is the presence of fat infiltrating the myocardium of the right ventricle. In spite of efforts to dissect off the fat, gross infiltration of the heart prohibits accurate myocardial weight estimation. As much as 20% of the ventricular weight may be due to fat, a fact which can be confirmed by weighing the ventricle after dissection and reweighing it after immersion in xylol for three to four days. It might be considered advisable to subtract a factor from the weight of the right ventricle in which there was much fat. However, the influence of fat between the fibres of the right ventricular myocardium is not a straightforward one and may itself cause atrophy or occasionally hypertrophy of the fibres.

Finally, a "normal" group of cases was selected (table III). Not only were the left and right ventricular weights considered, but also clinical, macroscopic or microscopic evidence of

of heart disease disqualified a patient from this group. Clinically, evidence of left ventricular failure was based mainly on a history of substernal chest pain at rest or on exertion, or paroxysmal nocturnal dyspnoea; alternatively, "right ventricular failure" was diagnosed mainly on the clinical findings of elevated jugular venous pressure, congestive hepatomegaly, and peripheral oedema.

It will be noted that in eight of the so-called "normal" group, manifestly hypertensive blood pressures have been recorded. In two of the eight, the combined left ventricular and septal weight is between 180 and 190 G., and almost certainly, the myocardium in these two cases is in fact mildly hypertrophic.

Minor discrepancies are inevitable in a biological study of this type if a particular value is used as an absolute dividing line between normality and abnormality.

Ventricular weights will reflect not only on alterations in the amount of myocardium but also any change in the fluid content of the muscle. Metabolic studies of water and electrolytes have shown that during the development of cardiac failure, the cells lose potassium and sodium and gain water because of activation of osmotically inert cellular base (Iseri et al. 1950). However myocardium, whether

from normal hearts, or hearts from patients in uncomplicated left ventricular failure or in congestive failure, were found by Iseri and his colleagues (1952) to contain about the same proportions of water. These workers analysed infarcted hearts and found that infarcted myocardium showed a marked but proportionate rise in sodium and chloride, reflecting a severe interstitial oedema. The analyses of distant blocks not grossly infarcted gave results of electrolyte and fluid content between the values obtained from infarcted segments and those from normal controls. The water and electrolyte content of the human heart was measured in congestive heart failure with and without digitalisation by Clarke and Mosher (1952). The water content of all normal, diseased and digitalised hearts examined was the same.

Thus, although in general, patients who die in congestive heart failure have heavier hearts than patients who do not, the increase in weight is due to an increase in the amount of myocardium and not to a significant increase in tissue fluid. Only in areas of acute infarction is there evidence of an increased fluid content.

No conclusive results were obtained to confirm the theory that after a critical ventricular weight, the cavity enlarges by increasing the number of its constituent fibres. Nevertheless there is a tendency in the graphs of the figures obtained which suggests that an upper limit of fibre size is reached at ventricular weights which are in the case of the right ventricle about 80% above the normal figure and in the left ventricle about 30% above normal. The actual figures also suggest that the large variation of fibre size at this level may be related to the presence of two populations of fibres. Another feature of note discussed in the section on morphological changes of hypertrophy, is the nuclear pleomorphism noted in hypertrophic myocardium.

The statistical significance and correspondence with an increase of ventricular weight of the fibre size has been proved by selecting special clinical sub-groups. These cases were selected on the basis of the clinical diagnoses only and as can be seen from table IV there is a remarkable degree of correspondence between the weights and fibre sizes of the ventricles. In other words, hypertrophy must have accounted for a large measure of the increase in weight of these cavities, any hyperplastic element not being

sufficiently pronounced to alter the significance of the figures.

For the left ventricle, the square of the increase in weight is equivalent to the increase in the fibre thickness ($dW = 2dF$). For the right ventricle the cube of the increase in weight is approximately equal to the increase in fibre thickness on the right side ($dW = 3dF$). Thus the heart as a whole increases in weight considerably more quickly than the thickness of the fibres increases. This, of course, is accounted for by a corresponding increase in fibre length.

By measuring the average distance between myocardial cell nuclei and the breadth of the fibres at the site of the nucleus in normal hearts from infants, children and young, the normal mechanism of growth can be studied. During normal post-natal growth of the myocardium, after the definitive number of cells has been laid down, the cells enlarge to become wider and longer, a remarkable constancy of the width to length ratio being maintained by the growing cells. Another constant in these hearts from subjects of different age groups is the Z band to Z band distance. Thus, growth of the myocardium must be brought about by an increase in the

number of the component sarcomeres in each myocardial cell.

During the process of growth an important change takes place in the distribution of the capillaries. In the heart of an infant there is a capillary for every four or five myocardial fibres (Wearn, 1928; Roberts and Wearn, 1941). This means that there are four or five fibres enclosed in each space of the capillary network. In the heart of the adult, on the other hand, there is a capillary adjacent to each muscle fibre, so that there is only one fibre in each space of the capillary network. Since the number of fibres is the same in the adult as in the infant there must be a four-fold increase in the number of capillaries in the left ventricle of the adult. It is interesting that in spite of the growth of the capillary network, the width of the spaces in the network is essentially the same in the heart of an adult as in that of an infant.

When the work of the heart is intermittently but repeatedly considerably increased, as in athletes or labourers who perform heavy physical work, the heart can increase in weight by anything up to 200 G by a process of physiological hypertrophy (Linzbach, 1947). The individual fibres become

thicker and longer.

According to Bohmenkamp (1929), however, the most important factor controlling the size of the heart muscle mass is not the work done by the heart but the systolic force of tension of the heart muscle fibres. From heart-lung studies it has been shown that when a ventricle is loaded by putting up the diastolic end volume, the force generated per unit cross section must increase. This is a statement of Starling's law. If the load is maintained the increased tension to which the individual muscle fibres are subjected, leads to a hypertrophy until the force generated per unit of cross section of myocardium returns to normal values for the same increased amount of work.

In an athlete, as it is the tension on the heart muscle fibre that determines its size, it is reasonable to assume that the severe training methods of top-class middle and long distance runners, oarsmen, boxers and so on, will lead to physiological hypertrophy. However, even the dedicated athlete must stop running to eat, drink and sleep, so that the myocardium, in the presence of a good coronary circulation, a healthy pair of lungs and a normal haemoglobin level, can only become hypertrophied to the physiological limit which is probably well below the critical heart weight. To some

extent the athlete's heart is maintained in a state of hypertrophy even when at rest, by an associated bradycardia. However, with a long lay-off, the athlete's heart diminishes in size, as, in the physiologically hypertrophic heart of the athlete, at rest the force per unit of muscle will be less than that of the normal myocardium and a relative degree of atrophy will result. Rats trained to run have shown that this does occur experimentally (Hort, 1951).

Pathological hypertrophy will result from the constant, inexorable, increased tension on the heart muscle fibres in patients with hypertension, aortic valvular disease, and so on. In hypertension or aortic valvular disease, a volume hypertrophy results. A larger than normal ventricular chamber in volume hypertrophy results in a residue of blood being left in the chamber after systole, the so-called residual blood volume. This is the type of hypertrophy sometimes called "Eccentric Hypertrophy". On the other hand, when the increased work is due to resistance to ejection as in aortic stenosis or hypertension, a pressure hypertrophy results with the ventricular chamber size remaining normal, or even becoming reduced, so that there is no residual blood volume. This is known as "Concentric Hypertrophy". In either case the total heart weight may reach 1,000 G. or more and the left

ventricle may reach a mass of 400 G.

The change from concentric to eccentric hypertrophy has been ascribed to "myogenic dilatation", when fibres become more and more stretched in diastole. However, Linzbach has studied this in a number of eccentrically hypertrophic hearts, and he has found no evidence of muscle fibre overstretching. The Z band to Z band distance remains on average 1.4μ. He also noted that the average distance between nuclei in the middle of a fibre is the same for eccentric as for concentric hypertrophied hearts of the same weight. From these basic facts Linzbach (1956) propounds that initially, dilatation occurs as a result of "plastic structural changes" within the myocardium, the rearrangement of the muscle fibres taking place in part radially across the wall, and in part tangentially with the wall for there is a smaller number of fibre layers across the wall in eccentric hypertrophy than in concentric hypertrophy when the total heart weight is the same.

The focal hypoxic necroses, commonly seen in eccentrically hypertrophied myocardium, may hasten dilatation. With increased systolic tension in the surviving fibres, the fibres which are hypoxic may then become overstretched during isometric contraction. This in turn will lead to overstretching of other

fibres, a situation which the Linzbach school have named "irreversible plastic dilatation." The residual blood volume is increased but in contrast with the normal heart and the athlete's heart, the increased residual blood volume cannot be mobilised. Thus two more terms have been introduced, the mobilisable residual volume of the athlete's heart and the fixed residual volume of irreversible plastic dilatation.

Linzbach believes that this type of dilatation occurs when concentric hypertrophy degenerates into eccentric hypertrophy, and is also seen in the volume hypertrophy of aortic insufficiency, especially when associated with endocarditis and myocarditis. Further, it would appear that the dilatation without hypertrophy seen with gross coronary atheroma is also of this type.

Electron microscopy has shown that in patients with mitral stenosis or atrial septal defects, dilatation of the cavity of the atrium is associated with distraction of the component laminae of the intercalated discs, "Dehiszenz Glanzstreifen" (Poche, 1958). This phenomenon has been seen in the hearts of animals poisoned by phosphorus and in hearts from starving animals (Poche, 1958). It is also constantly seen after cardiac arrest induced by potassium

citrate (Lohr, Meessen and Poche, 1960). Experience in the use of potassium citrate in cardiac surgery has shown that during or after induced cardiac arrest by this means small changes in blood pressure lead speedily to dilatation with fatal cardiac failure (Ross et al., 1958). This extraordinary hypersensitivity of potassium citrated hearts to stretching may be related to the presence of these distractions of the laminae.

It thus seems likely that two mechanisms are involved in dilatation. The sliding rearrangement of the heart muscle fibres on one another may be accompanied by distraction of the intercalated discs, a feature of ultrastructural dimensions not betrayed by internuclear measurements but nevertheless a significant one in view of the cellular nature of the myocardium.

Conclusion

From the heart weights and measurements of three groups of cases in this series, "normal", "L.V. hypertrophy" group and "R.V. hypertrophy" group, the number of observations in the upper range is too small to establish Linzbach's theory of critical heart weight. However, this work tends to confirm rather than to refute the

theory.

The fibre thickness figures have been tested for significance by means of selected clinical groups and the variance between the sexes and age groups has been established.

Normal heart growth, the classification of hypertrophy and its transformation from dilatation are discussed.

Morphological Changes in Hypertrophying Muscle

In 1903 Albrecht stated that in myocardial hypertrophy there is first an increase in sarcoplasm. Linzbach (1950) showed that growth in heart muscle fibres in hypertrophy occurs in a stepwise progression and that every single stage in that growth is due to an initial intake of water by the cells.

Human myocardium obtained from patients with mitral stenosis or an atrial septal defect has been studied in varying stages of hypertrophy (Poche, 1958). In hypertrophying myocardium there is an increase in peripheral subsarcolemmal sarcoplasm, with the result that the normal arcade formation of the sarcolemma becomes diverticulum-like. An expression of this growth is the finding of so-called ergastoplasm membranes, structures not normally seen in the heart muscle cells. A sign of increased metabolite transport is the increase of protomembrane vesiculation ("micropinocytosis" of Odor, 1956; or "cytopempsis" of Moore and Ruska, 1957). In the increased amount of subsarcolemmal sarcoplasm, many small vesicles and newly formed elements of the endoplasmic reticulum are seen.

In fully developed hypertrophy there is an increase in

the number of myofibrils and mitochondria in heart muscle cells. These myofibrils are not substantially increased in thickness. Rouiller and Bernhard (1956) and Poche (1958) found an increase in the number of "dense bodies" or "micro-bodies" in hypertrophying myocardium and it has been suggested that these are mitochondrial precursors. However, no definite transition from one to the other has so far been reported.

The myocardial transverse tubule system which Poche and Lindner consider to be invaginations of the sarcolemma, is much more distinct and wider in hypertrophic than normal muscle.

In experimental renal hypertension in rabbits, Molbert and Iijima (1958-59) showed that ten to fifteen per cent of the myofilaments in the periphery of the myofibrils are increased in thickness. At the same time they saw in developing hypertrophy a decrease in the number of inner membranes of the mitochondria of the heart muscle cells.

Micromeasurement of fibres reveals an increase in fibre thickness certainly until considerable hypertrophy of the ventricles has occurred. In this study it has not been possible to assess a critical heart weight for each

ventricle but as has been stated, as the ventricle weights rise the variation in size of the fibres tends to increase until, in the left ventricle at a 30-40% increase in weight and in the right ventricle at a 70-80% increase in weight, this variation in size is gross. Any further increase in size results in an evening out of fibre size suggesting, but statistically not proving, that the large fibres have in fact split.

Double nuclei, split nuclei and nuclei down which a cleft (fig. 157) is apparently developing are commonly seen in hypertrophic cells. The nuclear variation is frequently most striking and has merited comment from many authors. Henschel (1952) related the incidence of double nuclei to heart weight and found that there was very adequate support from these nuclear studies to suggest that splitting of fibres and nuclei occurred at or about the critical heart weight.

Another light microscopic feature of the hypertrophic myocardium is the density of the stroma. Reticulin patterns of hypertrophic myocardium show it to be thickened in relation to the degree of hypertrophy (fig.123). Reticulin in normal myocardium consists of fine strained branching

fibres which are slightly fuchsinophilic (on van Gieson staining); in hypertrophy, however, the thickened reticulin has a much stronger affinity for fuchsin. A pattern of "reticular fibrosis" is produced in some areas of hypertrophy in which the differentiation of collagen from reticulin is not demonstrable by histological means.

Another histological feature of hypertrophic myocardium is the prominence of the intercalated discs. This may be contributed to by some degree of distraction of the constituent laminae of the discs.

The Causes of Ventricular Hypertrophy of the Routine Autopsy Series

Retrospective diagnosis of the cause of ventricular hypertrophy is in many cases not easy. The causes of cardiac hypertrophy are those factors "which (1) either increase the resistance to outflow from the heart, (2) increase the inflow to the heart, or (3) produce severe myocardial weakness" (Friedberg and Sohval, 1937).

The Left Ventricle

Normotensive blood pressure readings taken on admission to hospital wards do not eliminate the possibility that patients are suffering from the cardiovascular wreckage which has been brought about by essential hypertension. It is a not uncommon experience to find advanced vascular nephropathy and cardiomegaly in a subject in whose case notes normotensive pressures are recorded. In addition to renal changes an index of essential hypertension is advanced intramyocardial coronary arteriolar change (Kathke, 1955). The remarkable degree of vascular change seen in the papillary musculature in particular (fig.137-140) is a reliable index of hypertension. Pyrexial disease may produce a degree of vasodilatation and general systemic upset which may mask a truly hypertensive blood pressure. Alternatively, the signs of left ventricular failure may have led to a patient's admission, normotension being in this case a reflection of his diminishing left ventricular power. A third group in which hypertensive blood pressure readings will be masked, are the patients admitted in shock.

The difficulties of accurate blood pressure recordings are considerable. Technique in the estimation of blood pressure varies considerably and indeed may vary from time

to time in the same medical attendant. Sphygmomanometers receive little attention and much ill-use, so that the results obtained in one ward with one machine may vary from the results obtained in the same ward with another machine.

However, this whole question is overshadowed by the fact that the nature of hypertension is by no means agreed. Pickering (Hamilton et al., 1954, a, b and c; Oldham et al., 1960) considers that essential hypertension is not a specific disease entity, varying blood pressures being distributed continuously throughout the population, as are height and intelligence. Those with so-called essential hypertension are merely an arbitrarily defined group, taken from one part of the distribution curve. Platt (1947, 1959) on the other hand considers that essential hypertension is a specific disease entity, some people having high and others normal blood pressure, according to whether they have the disease. The observation that the blood pressures of the siblings of a group of hypertensives had a bimodal distribution, indicating that two populations were involved is an important part of the evidence in support of the disease being due to a gene behaving as a Mendelian dominant character. It was suggested that these populations

comprised of those who had and those who had not, inherited the disease.

In the present routine autopsy series fourteen patients of the "L.V. hypertrophy" group had diastolic pressures of 85 mm.Hg. or over. In these patients hypertension is considered to have caused the hypertrophy. In ten of the "normal" cases, diastolic blood pressures of 85 mm.Hg. and over were recorded. Apart from two of these in which the combined left ventricular and septal weights were between 180 and 190 G. there was no doubt of the normality of the left ventricle.

Thus a diastolic pressure of 85 mm.Hg. or greater was recorded in twenty-four patients and was associated with hypertrophy of the left ventricle and septum certainly in fourteen or at the most sixteen of these.

In seven patients in whose case notes no blood pressure reading, a normal blood pressure, or hypotensive readings had been recorded, microscopic evidence of moderate to severe renal vascular disease and severe arteriosclerosis of intracardiac branches of the coronary arteries was seen. In these patients cardiomegaly is presumed to have resulted from hypertension which escaped diagnosis or had been present

before the terminal illness for which they had been admitted.

Thus in the forty-two cases of the "L.V. hypertrophy" group, hypertension has been a factor in the production of an increase in the myocardial mass of the left ventricle and septum in twenty-one cases.

An interesting experimental observation on heart changes in hypertension was made by Koletsky (1958). By giving rats 1% saline to drink instead of tap water he found that many of these animals developed hypertension, but all of them, whether hypertensive or not, had an elevated cardiac index (heart weight: body weight x 10^{-4}). The inference drawn from the experiment was that the salt had a direct hypertrophying effect on the heart as well as an indirect effect resulting from the association with hypertension.

In Experiment E it was confirmed that rats given 1% saline to drink will develop enlarged hearts but my method for assessing a rat's blood pressure was insufficiently accurate to assess the role of hypertension versus that of the salt itself.

Could it be that a diminution of the luminal diameter could cause a hypertrophy of the myocardium? Aschoff

(1933 b) refused to believe such a concept while Kaplan (1938) indicated that this was not an infrequent occurrence. Impaired nutrition causing dilatation was the mechanism suggested for the development of hypertrophy in association with coronary vascular disease on the evidence accrued by Davis and Blumgart (1937). In a study of the weight of hearts of soldiers dying of coronary disease, Yater and his associates (1948) also concluded that coronary disease alone may lead to hypertrophy of the left ventricle.

The answer to this problem is bedevilled by associated variables of which the most important is hypertension, and as already stated, it is seldom that the blood pressure state of patients with severe coronary disease is known before they are sufficiently ill to warrant admission to hospital. There seems little doubt that undiagnosed hypertension may act as the link between coronary vascular disease and hypertrophy.

Although the pathogenesis of atherosclerosis is still a matter of dispute it has been suggested that hypertension may contribute in two ways. Paterson and his co-workers (1960) have demonstrated a significant relation between blood

pressure and the degree of atherosclerosis found at necropsy in the cerebral and coronary arteries. They suggest that the high blood pressure ruptures the capillaries which frequently vascularise atherosclerotic plaques and so increases the deposit of blood lipids in the vessel wall. The other factor is that high blood pressure increases the rate of filtration of lipids from the lumen of the artery into the intima, for although in laboratory animals a raised blood pressure does not seem to influence the development of spontaneous atherosclerosis, it does aggravate cholesterol-induced atherosclerosis (Bronte-Stewart and Heptinstall, 1954). In the adult heart in which the left coronary artery arises from the pulmonary trunk, the coronary lumen is dilated, the wall is thinner than normal, the media has a poorly developed muscular layer and the intima has fibro-elastic thickening. The lack of atherosclerosis in such a vessel coupled with atherosclerosis in the right coronary, as Kaunitz (1947) points out, seems to indicate that there is a relationship between intravascular pressure and the development of atherosclerosis.

Arteriosclerosis and arteriolosclerosis occur in the intracardiac coronary branches. Hypertrophy of the media

and reduplication of the internal elastic lamina are characteristic and it is generally agreed that this type of change is entirely due to hypertension (Hueper, 1944).

The complications of studies on human material cannot be resolved but attempts have been made to assess the purely occlusive element of coronary artery disease in hypertrophy, by studying the effect of coronary ligation upon the hearts of experimental animals (Barnard, 1958; Norman and Coers, 1960). Norman and Coers found that in rats large healed infarcts were present in eight of eleven coronary-ligated animals killed six weeks after ligation and in all twelve coronary-ligated rats killed at twelve weeks. An increase in left ventricular weight was noted in the twelve-week group, this increase not being due to an increase in the water content of the myocardium. The conclusion was reached that the increase in weight represented cardiac hypertrophy, twelve weeks after coronary ligation.

Severe coronary atheroma was present in twenty cases of the "L.V. hypertrophy" group of the present series. In six of these, the coronary disease was the only abnormality found to account for the hypertrophy. In the remaining fourteen, evidence of hypertension or aortic valvular disease was present.

In the absence of arteriosclerosis and arteriolosclerosis, it seems reasonable to exclude the possibility that before admission to hospital these six patients had been hypertensive. On the histological and clinical evidence available, it is concluded that the reduced flow and consequent hypoxia which occurs as a result of coronary atheroma can lead to myocardial hypertrophy.

There is much clinical and experimental antagonism to the widely held thesis that a good blood supply is necessary for the development of hypertrophy. In chronic anaemia (Paplanus et al., 1958; Norman and McBroom, 1958) circulatory adjustments to some extent protect the myocardium from the hazards of hypoxia but it may well be that the hypoxia in itself leads to repeated episodes of dilatation which constitute the stimulus to hypertrophy. In cases in which there is an anomalous origin of the left coronary artery from the pulmonary artery, Kuzman and his colleagues (1959) state "the electrocardiogram is an important adjunct in the diagnosis for it characteristically demonstrates marked left ventricular hypertrophy associated

with "coronary type" T-wave changes." The pathological features in infants with this rare congenital anomaly are constant and consist of marked left ventricular hypertrophy and dilatation.

In two cases of the "L.V. hypertrophy" group of the present series (table I), severe anaemia (haemoglobin levels of less than 6.1 G/100 mls.) was the only demonstrable cause of the increased weight of the left ventricle. In one case a haemoglobin level of 11.2 G/100 mls. was the only abnormality found and in six cases levels of 11.2 G/100 mls. and less were recorded in patients in whom other causes of hypertrophy were found. In the "normal" group in seven cases haemoglobin levels of less than 11.2 G/100 mls. were recorded in the clinical notes. The nature of the primary disease in four of these cases (malignant disease in two and renal disease and ulcerative colitis in one each) suggested that the anaemia was of recent onset, but in the other three cases, all women, the haemoglobin levels varied from 8.96 G/100 mls. to 9.8 G/100 mls. and could well have been present for years.

Hypertrophy in man is thus a likely if not invariable result of chronic anaemia. Stembridge and Rigdon (1952)

have emphasised the lack of evidence which supports many of the reported cases of this association and reported only one case of cardiac hypertrophy in seven patients with sickle cell anaemia. However, Norman and McBroom reinvestigating the problem experimentally, found that in phenylhydrazine anaemia in rats, a cardiac hypertrophy resulted. They concluded that "the mechanism of hypertrophy under these conditions may be one of myocardial injury rather than mechanical."

The conclusion from Experiment G (page 374), in which by repeated venepuncture, Hooded Lister rats were made anaemic, was that a significant increase in myocardial mass was produced by hypohaemoglobinaemia of less than 7.30 G/100 mls. lasting five weeks.

The height and weight of the patient are factors which bear a significant relationship to heart weight. However, there is no unanimity that these two factors need consideration in heart weights in which pathological hypertrophy is demonstrable. By selecting the upper limit of normal at 189 G. it is hoped that these variations

due to height and weight have to some extent been eliminated. In a discussion on the weight of the human heart ("Normal Cases") Reiner and his co-workers (1959) studied the relationship of age and body weight to the weights of the right and left ventricles. The results from these hearts (it must be emphasised that they were selected for their normality), when plotted on scatter diagrams, indicated group differences in the sense that low values tended to be associated both with short stature and younger ages, while high values tended to be associated with both tallness and older ages. However, body weight was not significantly correlated with any of the component or composite cardiac weights. Only among the women was body height significantly correlated with the total cardiac muscle mass. These authors concluded that age did not influence the weight of the myocardium in adults.

Undoubtedly a physiological hypertrophy can result from athletic training and occupation, in physically exacting

work, but Reiner states that these constitutional aspects of body weight have not heretofore been correlated independently with total and fractional heart weights. He quotes that Zeek (1942) mentioned the element of body build by observing that persons (twelve out of five hundred and twenty-three males) with "unusually powerful muscular development" had heavier hearts than the remainder of the subjects categorised as either "emaciated", "normally nourished" or "obese". It is difficult to assess the "body build" or "degree of muscular development" and probably the answer lies in undertaking a project to relate heart weight to the body specific gravity, a figure which should reveal the obesity-leanness factor.

As is expected, in the present series there is a constant association between aortic stenosis and left ventricle hypertrophy, of which six examples were encountered.

A survey of causes of left ventricular hypertrophy in this series would be incomplete without considering the association between left ventricular hypertrophy and hypertrophy of the right side of the heart. Of the forty-two

cases of the "L.V. hypertrophy" group, in twenty-three this was accompanied by right ventricular hypertrophy. In twenty of the thirty-two cases in the "R.V. hypertrophy" group, left ventricular hypertrophy was also seen.

Chronic respiratory disease is seen commonly in hypertensives and so in some of these cases two sets of aetiological factors will exercise their influence to produce hypertrophy of both sides of the heart. Similarly in cases of co-existent mitral and aortic valvular disease, enlargement of the right as well as the left ventricle will occur.

However, chronic pulmonary disease itself must occasionally be a factor in the production of left ventricular hypertrophy. In many types of fibrosing pulmonary disease and especially in bronchiectasis, there is a great expansion of the bronchial arterial collateral circulation. (Liebow et al. 1949). The development of these shunts, the decreased efficiency of the respiratory blood pump causing a decreased oxygen tension, tending to increase the cardiac output, and an increased blood viscosity resulting from a secondary polycythaemia, must contribute to the production of left ventricular hypertrophy. However in only one case of the the "L.V. hypertrophy"

group has this association been seen. A chronic bronchitic man, aged 55 (N 3381), admitted in congestive failure was found to have a grossly enlarged heart. The left ventricle weighed 315 G. and the right 140 G. No clinical or post-mortem evidence of hypertension was noted and the valves of the heart were normal. The coronary arteries were only minimally atheromatous but chronic pulmonary disease was extensive. In two other cases (N 3396 and N 3476) chronic pulmonary disease was found in patients in whom left ventricular hypertrophy was present with right ventricular hypertrophy due to chronic pulmonary disease but in both of these, left ventricular enlargement could well have been accounted for by essential hypertension. On the other hand in seven cases of the "R.V. hypertrophy" group with chronic pulmonary disease, the left ventricle was within normal limits.

No other causes of left ventricular hypertrophy such as congenital heart disease, fibro-elastosis, arteriovenous aneurysm, hyperthyroidism, osteitis deformans or myocarditis have been encountered in this "L.V. hypertrophy" group.

The Right Ventricle

In thirty-two cases of the routine autopsy series, the free wall of the right ventricle weighed more than 69 G. and were selected for the "R.V. hypertrophy" group.

The most common cause of right ventricular hypertrophy is chronic pulmonary disease, the detailed study and increased understanding of which has led to the increasing use of the broad term cardiopulmonary disease. As Liebow states "This concept is wider than the usual connotation of "cor pulmonale"; but even the latter term has a vague boundary." The main difficulty with the euphonious term "cor pulmonale" is that for years it has been used as a cloak for the vagueness and speculation that has surrounded the basic mechanisms involved in the association between heart and lung disease, and it has finally come to grief by meaning different things to different people. Cournand and Richards and their associates use the term to mean disease of the right side of the heart, secondary to pulmonary disease (Ferrer et al., 1950), whereas others such as Dexter and his school (1951) include the effects upon the right side of the heart of increased post-capillary resistance occurring in mitral stenosis. However with an increasing volume of support suggesting that mitral

stenosis can cause spasm and in time narrowing of the pulmonary vessels, the use of the broader term is preferable for it does not purport to mean more than it says. Recently an astute medical student of our class of pathology was sufficiently confused by the different text books and taught interpretations of the meaning of the term "cor pulmonale" to draw her own interpretation (after Hoffnung) in our local student magazine, Chiasma, 1959 (fig. 100).

In ten of the thirty-two cases in the "R.V. hypertrophy" group, pulmonary emphysema was present. In association with emphysema were chronic bronchitis, varying amounts of pulmonary fibrosis, and terminal broncho-pneumonia. Why patients with emphysema should develop pulmonary hypertension is not clearly understood. In view of the reversibility of pulmonary hypertension in emphysema when the anoxia is relieved, the loss of capillary bed and irreversible changes in the larger vessels must rarely be the prime factors in its pathogenesis. The effects of anoxia, however, are considerable. There is good evidence to suggest that in pulmonary emphysema vasospasm is induced by hypoxia. In 1953 Harvey and his colleagues showed that pulmonary hypertension and congestive heart failure are gradually reversible in many patients if normal

or nearly normal alveolar oxygen tensions and systemic oxygen saturation can be achieved. Thus vasospasm in addition to loss of capillary bed may well be the operative factors involved in the production of a mild pulmonary hypertension which will lead to enlargement of the right side of the heart.

In the hearts of the three cases of mitral stenosis seen in the routine autopsy series, right ventricular hypertrophy was found. The elevation of pressure in the left atrium and pulmonary veins which occurs after elastic limit of these structures is reached (Sarnoff and Berglung, 1952) will contribute to a rise in pulmonary capillary pressure. Venous congestion in the lungs leads to haemosiderosis (Lendrum et al. 1950) and fibrous tissue proliferation in the lungs. The pulmonary vascular changes in mitral stenosis were described by Parker and Weiss (1936), and Heath and Whitaker (1955) indicated that the severity of arteriolar obstruction is proportional to the level of pulmonary hypertension, but Evans and Short (1957) interpreted the thick media of these vessels as evidence of their abnormal state of contraction.

Recently in lungs from cases of mitral stenosis Lendrum

(cited by Liebow, 1960) has shown that vascular lesions hitherto thought to be due to rheumatic pneumonitis may be attributed to the raised pressure within the pulmonary circulation. This acute focal vasculitis may be complicated by thrombosis and focal infarction of the chronically congested lung.

Thus pulmonary hypertension and consequent right ventricular hypertrophy in mitral stenosis is brought about by a complex of vascular and interstitial factors triggered by the venous congestion caused by a rise in left atrial and pulmonary venous pressure.

Pulmonary fibrosis was seen in one patient of the "R.V. hypertrophy" group in whom a lobectomy had been carried out for a bronchial carcinoma two and a half years previously. This operation was followed by radiotherapy.

In the hearts of just over sixty per cent of the cases of the "R.V. hypertrophy" group, left ventricular hypertrophy was also found to be present. As has been discussed, coexistence of factors producing right and left hypertrophy may account for part of this association.

However, it may be that the factors of left ventricular enlargement can result in the production of a hypertrophic right ventricle by way of the rise in intercavitary pressure in the left side of the heart. In a consideration of what Rodbard and his colleagues (1959) called "The Spherical Dynamics of the Heart", they pointed out that the two ventricular chambers normally eject approximately equal volumes of blood. Since the mean pressure in the normal right ventricle is only about 10 mm.Hg., the tension generated in the chamber is probably only about ten per cent of the tension in the left ventricle. Thus the tension generated by the normal right ventricle provides a mechanical support for the ventricular septum contributing to the strength of this wall and to the left ventricle as a whole. A process such as hypertension will result in an increased pressure within the left ventricle which applied to the septum may well cause a transmitted mechanical pressure in the right ventricle.

Another possibility is that as detailed in Chapter Four, the heart consists of five bands of muscle, three of which have components in both the left and right

ventricle. It seems unlikely that when hypertrophy of the left ventricle occurs, the process will stop dead in the muscle bundles at the right border of the septum. The continuity of the sarcolemma within the bundles and transference of the stimulus and metabolites leading to hypertrophy will surely extend some way round to the right ventricular myocardium. On the other hand it would seem less likely that a right ventricle undergoing hypertrophy could similarly cause a significant increase in the weight of the left ventricle which is functioning at pressures far in excess of even marked pulmonary hypertensive levels.

As can be seen from the "L.V. hypertrophy" group (table I) these mechanisms may well be present in many hearts but in fifteen (35.7%) of the forty-two examples in this group, the right ventricle weighed less than 60 G. However, a survey of causes of the left ventricular hypertrophy of these cases, compared with those of the cases in which left and right ventricular hypertrophy were seen together (in the absence of an obvious cause of right ventricular enlargement), reveals no correlation with any one mechanism.

In this "R.V. hypertrophy" group, the only other contributory factors to a right ventricular increase in weight were repeated pulmonary embolism (in two cases) and one case in which amyloid infiltration of the right ventricle was extensive. No example of pulmonary granulomatosis, diffuse pulmonary vascular disease (other than that of repeated pulmonary embolism and mitral stenosis), congenital heart disease or primary pulmonary hypertension was seen.

CHAPTER FOUR

Idiopathic Cardiomegaly

Since the original description of idiopathic cardiomegaly some sixty years ago (Josserand and Gallavardin, 1901), the cause of this condition has provided fertile ground for speculation.

The diagnosis is arrived at in normotensive patients in whom no intra- or extra-cardiac lesion can be demonstrated to account for the enlargement of the heart.

A strict application of this definition excludes many reported examples of this perplexing condition, and until a definite aetiology and pathogenesis can be proved, it is wise to study this disease "in as pure a form as possible" (Spodick and Littmann, 1958). It is agreed by most pathologists that advanced coronary disease, extreme myofibrosis and renal evidence of past or present hypertension precludes the diagnosis of idiopathic cardiomegaly. However, there is less agreement on the exclusion of cases in which enlarged hearts are encountered in association with aortic hypoplasia. Hayes and his co-workers (1959) suggest that the aortic changes are secondary in nature and it is difficult to find fault with their argument. However, the fact

is, that many cases have been reported without this feature and it is these examples which must be considered if the definition is to be observed. It is interesting, on this question of exclusion of cases, to recall that in reviewing many reported cases of idiopathic cardiomegaly or idiopathic hypertrophy, as some prefer to call it, Weinberg and Himmelfarb (1943), impressed by the striking endocardial thickening in more than half of these cases, called this group endocardial fibroelastosis.

Recently an opportunity arose to study the heart of a young girl in whom the diagnosis of idiopathic cardiomegaly was made and the chance was taken to evaluate a pathogenetic theory which has not previously been reported. The case report, clinical, operative and post-mortem findings are given in Appendix C (Volume II).

A Case of Idiopathic Cardiomegaly.

The heart of this girl was first noted to be abnormal at the age of four years, following measles. The abnormality was rediscovered at the age of eight years when she was admitted to hospital with miliary tuberculosis. After recovery she was found to be sensitive to penicillin, after the injection of which her mother stated that she suffered

"heart attacks". By the time the case notes were reviewed it was impossible to question the mother on this point and it can only be assumed that these "attacks" consisted of palpitation or discomfort in the chest. At the age of ten, a polyarthritic febrile illness was diagnosed, following which she had a number of mild recurrences. The description of the disease defies a diagnosis other than rheumatic fever. A tonsillectomy was carried out at the age of twelve.

It was soon after this that signs of cardiac decompensation were evident. She became easily breathless, was mildly cyanosed on exertion and by the age of fourteen years she was considerably handicapped. After cardiac catheterisation she was considered to have a combined mitral and tricuspid stenosis and finally at operation under hypothermia no abnormality could be found in the heart to account for her gross cardiomegaly. She died after this operation. At autopsy the heart weighed 590 G (figs. 101 - 103) and as can be seen from the photographs, both the left and right ventricles were hypertrophic. I am indebted to Professor J. Schoenmachers for a copy of the report of the autopsy (details of which are given in Appendix C, Volume II) who

summarised his findings as right and left myocardial hypertrophy (?myocarditis), cirrhosis of the lungs, and cardiac cirrhosis of the liver. Death was due to cardiac insufficiency.

On microscopy the myocardium was extensively focally scarred and in many areas focal myocytolysis and healing areas of focal necrosis were seen. However, the valves were normal as were the coronary arteries which arose normally from the aorta, and there was no evidence of a rheumatic process, past of present, in the histology of the myocardium. The pericardium showed evidence of recent inflammation due to the operation but was not extensively fibrosed.

None of the causes of myocardial hypertrophy were demonstrable, either in life or at autopsy. Hypertension was excluded by repeated normal blood pressure recordings (and the renal histology was in agreement with this), no valvular abnormality was demonstrated, the septae were imperforate, and the coronary vessels were healthy. It should be particularly noted that angiography failed to reveal a stenosis of the outflow tract.

The clinical course and pathological findings in this

case are fairly typical of the ill-understood but widely recognised entity "Idiopathic Cardiomegaly". From the reviews of Norris and Pote (1946) and Serbin and Chojnacki (1955), Spodick and Littmann (1958) and others, this disease is rare. It is most commonly seen in later childhood or early adult life, and a greater incidence has been noted in males than females. The myocardium has been variously described but the findings in this case are typical of most. One commonly noted feature which was not seen in this case was mural thrombosis. Endocardial thrombosis and embolic phenomena have frequently been reported in cases of this type, and if this does not prove fatal then patients usually die in congestive cardiac failure.

Causal Hypotheses

(a) Genetic Theory. There is undoubtedly a strong genetic factor involved in the aetiology of many cases of idiopathic cardiomegaly. The familial form of this disease was described first by Evans, (1949). The clinical course and pathological findings are almost identical to those of the non-familial form. Of considerable interest in this connection is a paper by Teare on "Asymmetrical

Hypertrophy of the Heart in Young Adults" (1958), in which case 5 and the boy mentioned in the addendum were brother and sister. In a covering letter with a reprint of this paper, Dr. Teare mentioned that further investigation had revealed "that several siblings in this family who have or may have the same condition have been discovered." However attractive the genetic theory may appear it is applicable to less than half of the reported cases of idiopathic cardiomegaly. In the case studied there was no suggestion of familial heart disease.

(b) Previous myocarditis. That idiopathic cardiomegaly is related to a passed bout or bouts of myocarditis is probably the most widely held theory and the most difficult either to prove or disprove. One of the points of interest in this case is that not only is there a past history of infectious fevers after one of which the child was noted to have an abnormal heart, but also of course, she had repeated clinical episodes of rheumatic fever. The endocardium and myocardium, however, showed no evidence of rheumatic involvement. The scarring of the myocardium could undoubtedly result from an old myocarditis, but hypertrophy and bouts of left ventricular failure could well account for the changes seen.

The acceptance of a myocarditic cause for idiopathic cardiomegaly precludes further thought on the subject. Some years ago it was suggested the influenzal pandemic of 1918 was responsible for the appearance of idiopathic cardiomegaly cases appearing in the late twenties and early thirties. However, von Bonsdorff (1949) reviewing "many hundreds of autopsies in influenza and grippe" considered this hypothesis highly unlikely.

(c) Metabolic and Deficiency Theories. Potassium deficiency, vitamin B deficiency (Dock, 1940), and endocrine disease have been suggested as possible aetiological agents but in the absence of related clinical and pathological abnormalities, their role in the production of gross cardiac enlargement must be remote.

(d) Functional and Developmental Theories. The myocardium of the ventricles consists of five muscle bundles (McCallum, 1900; Mall, 1911; and more recently Puff, 1960). The scroll muscle is the muscle of the apex. The other four bundles consist of a superficial and deep group (fig. 104). The superficial bundles possess an internal portion which constitutes the papillary muscles.

Physiologists agree that the time of initial negativity of the interior and exterior of the apices of the two ventricles is early. Rappaport and Sprague (1942) reported that heart sounds were present during the period of isometric contraction. These facts give physiological and anatomical support to the conception that the superficial muscles have two definite functions, to fix the apical fulcrum and to fix the atrioventricular valve leaflets (Robb and Robb, 1942). It would be impossible to have a period of rising tension with isometric contraction unless the ventricular cavities were closed. To prevent the atrioventricular valves from bulging into the auricles, thus allowing regurgitation, the valve flaps must be fixed and, therefore, the papillary muscles must be contracted to keep the chordae tendineae tense. Early contraction of the superficial muscles is also required to prevent an aneurysm of the apex where the wall is as little as 1 mm. thick.

The deep sino-spiral muscle must be responsible for the maintenance of the pulmonary circulation. The left portion of this muscle is also large and because of the direction of its fibres can have no other function than the expulsion of blood. The deep bulbo-spiral muscle

contracts late and completes the emptying of the left ventricle. This bundle supports the blood column in the aorta and when it relaxes, the aortic valves fall back into position to maintain diastolic pressure. If the bulbo-spiral muscle contracted early it would produce a narrowing of the aortic outlet, a functional stenosis.

This is a possible cause for idiopathic cardiomegaly. Two patients have been reported by Morrow and Braunwald (1959) in whom the clinical findings of aortic stenosis were present and a pressure gradient was demonstrated between the left ventricle and the aorta. At operation no anatomical site of outflow obstruction could be detected. It was concluded that the obstruction to ventricular outflow was of such a nature that it is only operative in a contracting heart and was not apparent during the diastolic paralysis induced by potassium citrate at open heart operation. These features could be explained by muscular hypertrophy of the left outflow tract of sufficient severity to impede flow during contraction, or premature contraction of the bulbo-spiral bundle and its secondary hypertrophy. Functional obstruction to ventricular ejection is not a new concept. A systolic pressure gradient across the outflow tract of the right ventricle

may develop as a result of severe right ventricular hypertrophy associated with such lesions as stenosis of the pulmonary valve or ventricular septal defect (Kirklin et al., 1953; Brock, 1955; Campbell and Brock, 1955; Himmelstein et al., 1957; Engle, 1958; Gasul et al., 1957). Proof that many of the examples of this form of obstruction are of a secondary nature is provided by the observations of Gasul and his colleagues who noted its development in patients with ventricular septal defect, and stated that an increasing number of papers report the regression of the subvalvular gradient when the primary stimulus to ventricular hypertrophy is removed. Nevertheless, examples of muscular subvalvular outflow tract stenosis are not always secondary to anatomical defects and by no means is such a stenosis always demonstrable after death. It remains to be seen if a primary defect of impulse conduction causing premature contraction of the bulbo-spiral bundle (for left ventricular hypertrophy) or sino-spiral bundle (for right ventricular hypertrophy), or both, can be incriminated as a cause of at least some of the cases of idiopathic cardiomegaly. This theory would best be tested mapping the distribution of conducting tissue in these hearts, or by direct intramuscular electrocardiography. A more clinical

approach would be to inspect the graphic registration of the heart sounds or perhaps to have recourse to the ballistocardiograph. In theory at least this last aid should provide the answer.

Another possibility as a cause of idiopathic cardiomegaly is a maldevelopment of the heart, which results in a disorientation of the constituent parts of the muscular bundles. The superficial bulbo-spiral bundle (fig. 104) arises from the conus, left side of the aortic septum, aortic ring and left atrioventricular ring, passes apicalwards and somewhat towards the right to the posterior horn of the vortex of the left ventricle (figs. 105 and 106). At their origin, the fibres form a broad thin sheet that becomes thick and narrow at the apex where the bundle twists on itself and continues upwards in a spiral manner on the inner surface of the left ventricle, spreading out into a thin sheet that is inserted on the opposite side of the tendinous structures from which it arose. These fibres make nearly a double circle round the heart, like a figure of eight that is open at the top. As the fibres pass towards the apex they lie superficial to the deep bulbospiral bundle and as they pass upwards from the apex they partly blend and partly pass on the inner side of it

in a direction nearly at right angles to the superficial fibres.

The superficial sino-spiral bundle arises as a thin sheet from the posterior aspects of the left and right atrioventricular rings and from the right side of the latter. The fibres pass more horizontally around the heart to the apex than do those of the bulbo-spiral bundle (fig. 105). They pass completely around the right ventricle, across the posterior and anterior longitudinal sulci, gradually converging as they approach the apex and enter the anterior horn of the left vortex as a narrow thick band that twists upon itself to encircle the apex as it passes upwards into the papillary muscles and the inner wall of the left ventricle to become attached to the fibrous rings either by the chordae tendineae and the valve leaves or directly by the fibres themselves. These fibres likewise course around the heart somewhat in the form of a figure eight that is open at the top with a small loop at the bottom. As the bundle enters the vortex it is joined by fibres from the longitudinal bundle of the right ventricle and fibres of the interventricular bundle from the papillae of the right ventricle. Many of these pass into the papillae of the left ventricle.

Many fibres from both bulbo- and sino-spiral muscle bundles enter the interventricular septum as they pass into the anterior longitudinal sulcus.

In the cephalic halves of the ventricles the two parts of each superficial muscle are normally directly opposed to one another. If there was not a direct opposition of the constituent parts these muscles would work at a mechanical disadvantage and the effort of the deep muscles would have to be the greater to do a normal amount of work. A resultant effect would be hypertrophy.

Variations of disorientation would have variable results. Bilateral involvement of the superficial musculature would result in a concentric hypertrophy of left and right ventricular cavities, but if the disorientation was of one muscle only, variations of asymmetrical hypertrophy could result. In this connection, the paper by Teare on asymmetrical hypertrophy of the heart in young adults is of considerable interest. Another case of this type was the subject of a clinico-pathological conference held at the Medical Academy, Düsseldorf (Meessen, 1959). This was a ten-year-old boy in whom a diagnosis of pulmonary stenosis or more exactly infundibular stenosis was made by means of cardiac catheterisation. The

stenosis was due to a massive hypertrophy of the ventricular septum which had bulged into the outflow tract. The heart was greatly hypertrophied and weighed 510 G. There was no localised tumour such as rhabdomyoma which might have distorted the structure of the myocardium. Both ventricles were hypertrophied but there was no atrial or ventricular septal defect and indeed no congenital anomaly of any kind could be demonstrated.

These functional theories of early bulbo-spiral contraction and disorientation of bundle arrangement are extremely difficult to prove after death. Functional aortic stenosis is now recognised as a clinical entity, and in life by means of electrodes placed within the myocardium in various sites, it should be possible to demonstrate abnormalities of timing in the contraction of the various bundles. After death, it may be impossible to see any evidence of stenosis. In a few cases (such as the subject of the clinico-pathological conference) there is a localised hypertrophic area which may be apparent as the cause of the stenosis, but in many, no such signs are seen, these cases being diagnosed as "Idiopathic Cardiomegaly."

If disorientation of the muscle bundles is a cause of some of the examples of this disease, dissection will be the only means by which this can be proved. The heart of the case reported here was received in three horizontally sliced pieces (figs. 101 to 103). In such a state it was considered impossible to dissect off the constituent bundle layers (Puff, 1960); however, large horizontal sections of the whole heart were cut from four levels, and small blocks from each of these levels from the whole circumference of the heart were cut and numbered. By means of a dissecting microscope it was possible to trace the direction of the fibre bundles at all four levels and the drawings of the composite pictures which emerged are shown in figs. 107-110. The constancy of the pattern at each level is no more than would be expected on naked eye examination of the heart. However, one feature of this heart that has not been seen in the hearts of other patients with bilateral ventricular hypertrophy is a lack of an oblique component running over the right ventricle. In horizontal sections from the right ventricles of normal hearts this oblique running fibre arrangement may be inconspicuous but in hypertrophy oblique fibres are thicker and more prominent than normal. The thickened right

ventricle of the case of unexplained heart enlargement showed only horizontal, or nearly horizontal, and vertical components. This is a feature of which confirmation from other cases of this type is essential before its significance can be assessed.

By this method of examination, it was not possible to recognise the constituent parts of each superficial muscular bundle, so that an investigation of their orientation demands serial sectioning of the whole heart or dissection by stripping the muscle bundles from the epicardial surface. In neither case is this an easy procedure. It must be remembered that this is a rare disease which demands adequate examination of the heart before the diagnosis can be made, so that it is unlikely that the anatomist could be given such a heart intact, or sufficiently so, to allow the dissection of the constituent bundles. On the other hand, serial sectioning of the heart to extract the information required would be extremely difficult. Probably a combination of dissection and the charting of fibre directions from serial sections would reveal enough information to indicate the validity or otherwise of the theory of disorientation of

the constituent parts of the superficial musculature.

A possible mechanism of development of idiopathic cardiomegaly was suggested by Black-Schaffer and Turner (1958). They considered that from a combination of nuclear density assessments and fibre thickness measurements, an extra generation of heart muscle cells might account for an enlargement of the heart. There is no doubt that there is an infantile group of examples of idiopathic cardiomegaly. Although many of these cases have now been reclassified as examples of glycogenic storage disease, endocardial fibroelastosis, medial necrosis of coronary arteries or aberrant coronary artery (Rosenbaum et al., 1953) a number of cases of unexplained cardiomegaly remain. Whether an infant in whom the number of cardiac cells is grossly in excess of normal can survive to early adolescence is very doubtful and in the case reported here, the nuclear density of the myocardium was comparable with the four hearts of the routine autopsy series of comparable weight.

CHAPTER FIVE

Relative Myocardial Hypoxia

The history of hypoxic heart disease starts in Italy where Giovanni Maria Lancisi (1654-1720), a Professor of Anatomy, published two volumes on the heart. In "De Subitaneis Mortibus" (1707) and "De Motu Cordis et Aneurysmatibus" (published eight years after his death) Lancisi described heart disease as one of the common causes of sudden death and gave good descriptions not only of sclerotic and warty valves but also of the coronary system. Among the causes of hypertrophy he listed calcified arteries.

William Heberden, on July 21st 1786 gave a lecture to the Royal College of Physicians on "Angina Pectoris". This lecture was published four years later and is a brilliant clinical description of the clinical syndrome. However, in "Syncope Anginosa" (1799) Caleb Hillier Parry got much nearer the truth of the cause of the clinical symptoms and gave the first description of what many years later came to be called coronary insufficiency. Also there seems little doubt that Edward Jenner at this time not only recognised a correlation between coronary artery disease and disease of the myocardium but realised that

his teacher, John Hunter, actually suffered from the syndrome.

In the FitzPatrick Lectures (published in 1957), given before the Royal College of Physicians, East related that in Glasgow, a young man Allan Burns, a member of the Royal College of Surgeons but with no medical degree, was an avid reader of Parry's work. Burns spent most of his time helping his brother teaching anatomy, and in 1809 published a book "Observation on Diseases of the Heart". He stated that if a limb round which a moderately tight ligature has been passed is exercised "we find then that the member can only support its action for a very short time; ...A heart, the coronary vessels of which are cartilaginous or ossified is in nearly a similar position; it can, like the limb, be girt with a moderately tight ligature, discharge its function so long as its action is moderate and equal. Increase, however, the action of the whole body and along with the rest, that of the heart, and you will soon see exemplified the truth of what has been said; with this difference, that as there is no interruption to the action of the cardial nerves, the heart will be able to hold out a little longer than the limb." Intermittent claudication in man

was not described until 1855 by J.M.Charcot and although Burns does not stress pain, he concluded that "When, therefore, the coronary arteries are ossified, every agent capable of increasing the action of the heart, such as exercise, passion and ardent spirits must be a source of danger."

As East points out, after such accurate and clear accounts of coronary heart disease by Heberden, Parry and Burns it is the more curious that the subject was fogged and confused for years to come.

With the development and increasing use of the microscope, the criteria for inflammation became established and myocarditis was recognised in acute and chronic forms. Unfortunately many of the great pathologists of the nineteenth century were so bemused by these inflammatory changes that they were unable to lift their eyes from their sections to the post-mortem room where sclerosis and thrombosis of the coronary vasculature had been seen. It seems incredible that men like Virchow and Rokitansky, of such vast experience of post-mortem appearances, not only failed to recognise the relationship of coronary artery disease and myocardial infarction, but failed to

be convinced by the stream of literature on this association, produced by Carl Weigert (1880), Karl Huber (1882), Ernst von Leyden (1884) and Ernst Ziegler (1887).

In this country, in 1887, J.L.Steven of Glasgow wrote a series of papers drawing attention to what he called "Fibrous transformation" in the heart. He noted fatty and fibrous lesions and infarction and rupture of the ventricles. He maintained that these lesions were definitely not due to inflammation and certainly not to "chronic interstitial myocarditis". In the British Medical Journal of 1893 a case report and discussion (in which Steven took part) published by G.A.Gibson and Robert Muir, tell the story and describe the pathological findings of a man, aged thirty-six years, admitted in cardiac failure and thought to have mitral and tricuspid incompetence. At autopsy this man was found to have cardiac fibrosis as a result of partial coronary obstruction. The authors reported this case in more detail the following year in the Edinburgh Hospital Reports and in their discussion they state, "The importance of the coronary arteries in relation to the nutrition of the heart wall has long been recognised but it is only within

comparatively recent years that the relationship of certain of these lesions to one form of so-called interstitial myocarditis has been established ..." (they quote the references to Weigert, Huber, Ziegler and Steven) ... "When the branches are the seat of chronic endarteritic change they may become obliterated or they may be thrombosed and infarcts result in the heart wall - soft, somewhat necrosed areas, which form the condition known as myomalacia cordis."

Progress from the days of Heberden was slow. In the Lumleian lectures given by Sir William Osler in the Royal College of Physicians in 1910, he included a discussion of myocardial disease resulting from coronary occlusion. Osler remarked that had Heberden listened to his first lecture he might have commented "Well, they haven't got much further since my day!"

However it was in that same year, 1910, that Obrastzow and Straschesko wrote their historic paper "On the Recognition of the Thrombosis of the Coronary Arteries of the Heart." They reported three cases of which two were diagnosed in life. Two years later J.B.Herrick's paper established the disease as a clinical entity recognisable in life and not necessarily fatal.

Today it seems astonishing that only thirty-eight years ago Wearn wrote "Coronary thrombosis with infarction of the heart as a clinical entity is a condition which is generally classed among the rarities in medicine."

Myocardial infarction is nowadays a common disease and the most common pathogenetic factor of infarction of the myocardium is atheroma. Thrombosis may complete the partial luminal obstruction caused by atheroma and probably never occurs in a normal coronary artery. It may appear somewhat surprising, therefore, to read good evidence which suggests that the increase in the incidence of myocardial infarction does not appear to have been paralleled by an increase in the amount of coronary atheroma. Indeed there is evidence that the incidence of coronary atheroma may have declined in this country during the past forty years (Morris, 1951). Coronary disease cannot be equated invariably with myocardial damage, and if the rise in the incidence of myocardial infarction is related to factors other than coronary atheroma, these factors are given too little space in the textbooks and minds of doctors.

A widespread acceptance of the association of coronary vascular disease with myocardial infarction, coincided with an absolute increase in the incidence of myocardial

infarction. The wisdom of men like Parry was soon forgotten. The frequency and ease with which infarction and coronary thrombosis were demonstrably related were too attractive to avoid the two terms becoming interchangeable.

Thrombosis of an atheromatous artery is but one of the many factors which may be responsible for myocardial changes, but to equate occlusive disease of a coronary artery with myocardial infarction is as inaccurate as it is an over-simplification. Intercoronary anastomoses may very adequately overcome the disadvantage of thrombosis and, or, severe atheroma of a coronary artery. Anastomotic channels (greater than 40 μ in diameter) were found in the majority of normal hearts examined by Prinzmetal and his colleagues (1947). In cases with occlusive coronary artery disease Pitt (1959) found that anastomoses were present in "75 to 100 per cent of the cases", and he demonstrated anastomosis in 43 to 50 per cent of the hearts of patients with hypertensive heart disease and valvular lesions. These results were obtained by injecting wax spheres (35-45 μ and 75-90 μ) into one coronary artery at a maximum pressure of 100 mm.Hg. and confirmed the results of Schlesinger (1938) and Zoll

and his colleagues (1951) who used an injection and X-ray method followed by dissection.

Thus occlusion of a coronary artery will not be followed by a specific series of events; if anastomosis is adequate only the mildest degenerative changes or perhaps no change at all will occur, but if the vasculature supplying the anastomotic channels or the channels themselves are grossly narrowed necrosis of the myocardium will ensue.

Conversely of course any of these hypoxic degenerative changes may occur in the absence not only of thrombosis but also of any disease whatsoever in the coronary vasculature. Disseminated areas of myocardial necrosis in persons who had had attacks of angina in the last days of their lives but who had not suffered a coronary thrombosis were described by Büchner (1939). Friedberg and Horn (1939) published a series of thirty-four cases of acute myocardial infarction without coronary thrombosis, found in a series of two thousand autopsies performed in the Mount Sinai Hospital over a period of four years. It is interesting to note that twenty-eight of their cases occurred in the last thousand and only six were found in

the first thousand cases. The coronary arteries were transected in great detail and narrow portions were taken for microscopic examination; cases in which occlusions were demonstrable were excluded from the series. The myocardial lesions in both of these series were in the main confined to the wall of the left ventricle and its papillary muscles.

The importance of hypoxia in the myocardium lies not so much in its absolute as in its relative level. It is the disproportion between what oxygen is required and what is available that determines not only whether an injury to the myocardium will be inflicted but also the grade of that injury. Hypoxia in absolute terms will be dependent upon mechanical factors which reduce the lines of supply of oxygen, the coronary factors, and by the physical factors affecting the oxygen carrying power of the blood, the haematological factors. The effect of this absolute hypoxia will finally be determined by its relation to the myocardium, its mass, its metabolic state and the efficiency with which it can use what oxygen is available. These have to be called myocardial factors.

The causes of relative myocardial hypoxia are summarised in fig. 111.

The routine autopsy series has been reviewed and of

the one hundred and twenty-five cases, in the hearts of sixty-two patients pathological changes of relative myocardial hypoxia were found. The causes of hypoxia in this "relative myocardial hypoxia" group (summarised in table V) will now be discussed, following which the wide gamut of histological changes which were seen will be described.

The Factors of Relative Myocardial Hypoxia

Coronary Factors

The method of coronary dissection is detailed on pages 7-11.The accuracy of this method of assessing the state of the vasculature has to some extent been called into question by the introduction of injection techniques. However, on a clean dry board, using sharp dry instruments, careful dissection must rival the accuracy of injection techniques in so far as the main coronary arteries and their primary and secondary branches are concerned. Histological confirmation of macroscopic abnormalities is essential as is an adequate and accurate description of the vasculature and labelling of the blocks as the dissection is being carried out. As suggested in fig.111, the coronary factors may be considered under various headings.

(a) Congenital Coronary Artery Abnormality.

Absence of one of the two main coronary arteries, with the entire heart supplied by a single coronary artery is one of the rarest reported congenital cardiac anomalies of practical clinical significance. In a review of this

subject Roberts and Loube (1947) discussed twenty-two cases in the literature and reported nine more. In one of the previously reported cases thrombosis and occlusion of the single coronary artery had occurred with the production of myocardial infarction, while among the adult cases of Roberts and Loube, there were three with myocardial infarction. Although this anomaly is compatible with normal cardiac function, these patients are at greater risk because all the available intercoronary arterial anastomoses are dilated and utilised early in life. In the event of a coronary artery thrombosis, no further compensation is available.

In 1959, Cohen and Siew reported a case of aberrant left coronary artery arising from the pulmonary artery, and reviewed forty-five cases from the literature. Three more examples of this anomaly were reported by Kuzman and his co-workers (1959), who considered that open heart surgery with transplantation of the anomalous vessel to the aorta is the treatment of choice.

It has always been something of a mystery that some patients develop an adult form of this malformation and are essentially asymptomatic while the majority die in

infancy with essentially the same defect.

It has been shown by Keith (1959) that if the pressure in the pulmonary artery is high enough to overcome the arterial and capillary resistance of the left coronary artery, the direction of flow will be normal delivering blood into the coronary sinus. At best, however, such a coronary artery arising from the pulmonary artery will be receiving venous blood at a relatively low pressure. If, however, the collateral circulation from the right coronary is sufficiently large, the direction of flow may be reversed and the anomalous left coronary artery acts as a vein conveying the blood to the pulmonary artery. At birth when the pressure in the right ventricle and the pulmonary artery is at, or near, systemic level, the flow will be in the normal direction. As the pressure falls in the right ventricle and the pulmonary artery in a matter of hours or days after birth, the flow will diminish until it approximates to that coming from the right coronary via the collaterals. In infants with this anomaly who have heart failure, the pressure may become raised again in the pulmonary artery to a degree that will permit a flow through the anomalous coronary in the usual direction. By angiocardiographic studies, Keith concluded that his evidence

suggested that the flow through the aberrant left coronary artery, whether in the conventional or in the reverse direction, is small and offers little or no nourishment to the tissues supplied by it. When the collateral circulation from the right coronary is poor, severe myocardial degeneration and fibrosis will occur and lead to early death. When it is large, survival is possible into adult life.

In this series there was only one case, a 66-year old female (N 3602) in whom a congenital anomaly of the coronary vasculature was noted. On dissection of the heart it was found that two vessels arose from the left anterior coronary sinus of the aorta. These arteries pursued the course of the anterior descending and left circumflex vessels. However, 1 cm. from the origin of the anterior descending branch arose a large (8 mm. circumference) vessel which coursed over to the right side of the heart in the distribution of the right coronary artery. The right anterior aortic coronary sinus contained no evidence of the origin of a vessel. At autopsy the left papillary musculature showed the signs of acute infarction. The vasculature generally was moderately atheromatous. Left auricular appendage thrombosis was present as were foci of hypoxic degeneration in that auricular

muscle; the patient was diabetic and as a result of atheroma and arteriosclerosis developed gangrene which necessitated the amputation first of a toe and finally a leg. Resuturing involved a third anaesthetic for this patient. She was mildly dehydrated and shocked when she finally collapsed, and died fourteen hours later.

In such a case it is difficult to estimate the significance of the congenital abnormality of the origin of the coronary vasculature in the production of relative myocardial hypoxia. The filling pressure of such an anomalous right coronary artery will to some extent be reduced, and the tendency to atheromatous narrowing of its ostium may differ from that of an aortic ostium. However, in many of the reported cases of this type of defect, the cause of death has been almost certainly unrelated to the congenital anomaly of the coronary artery, and in those in which it is incriminated as a cause of myocardial hypoxia, coronary atheroma and other factors diminish the likelihood that the congenital anomaly was the main factor causing death.

According to Krumbhaar and Ehrich (1938) who reviewed this subject, Hyrtl (1841) set the criterion for a true

single coronary artery by stating that the entire heart must be supplied by one coronary artery from which no conspicuous anomalous branches arise. Therefore a case such is reported here should not then be regarded as a true example of single coronary artery.

The risk to which a patient is exposed by the congenital absence of a coronary artery must be inversely related to the adequacy with which the vessel is replaced by a branch or branches from the artery present. In the case described, this risk was slight.

(b) Acquired Coronary Artery Abnormality.

i. Aortic Valvular Abnormality.

Dilatation of the aortic valve ring, as seen occasionally in association with a congenital high ventricular septal defect, Marfan's syndrome or with an aortitis may contribute to relative myocardial hypoxia in a number of ways. The effect upon the coronary vasculature is related to the altered pressures brought about by aortic dilatation preventing optimal coronary filling.

However, much more commonly, rheumatic, atheromatous or bacterial disease of the aortic valve and its resultant incompetence contribute to the relatively poor coronary

supply. Eight examples of these three diseases of the aortic valve have been seen in this series together with clinical evidence of aortic incompetence and a secondary left ventricular hypertrophy, a relative hypoxia producing factor which demands consideration in its own right (pages 147 - 153).

ii. Coronary Ostial Abnormality.

Direct involvement of the coronary ostia can result from the processes which affect the aorta or its valves. Syphilitic aortitis may not only result in dilatation of the aorta and aortic incompetence, but may also cause ostial stenosis as a result of the replacement fibrosis which occurs after medial destruction caused by this chronic granuloma. Non-specific primary arteritis of the aorta (Costel's Disease) usually involves not only the aorta but the branches of the aortic arch in which thrombosis can occur. Also associated with the medial disease is a uniform intimal fibrous thickening of the thoracic part of the aorta in which the coronary ostia may be involved. A dissecting aneurysm of the aorta may result in coronary ischaemia.

Of the diseases affecting the valves rheumatism probably always causes some degree of aortitis. Bacterial endocarditis may result in such a luxuriant growth of vegetation that direct ostial occlusion results. Finally, and most commonly of this group of coronary ostial diseases, atheroma which may involve the aortic valves, but much more likely, the aorta itself, may cause marked narrowing of the origin of the coronary arteries.

In one of this group of cases (N 3689) in whom dissection of the heart revealed an aortic stenosis (considered to be atheromatous in origin), atheroma resulted in the production of a raised stenosing lip round the origin of the right coronary artery, the ostium of which was reduced to about forty per cent of normal diameter. The coronary vasculature in the main trunks and branches was almost free of any evidence of arterial disease and yet, relative myocardial hypoxia had been severe enough to cause angina of effort for five years and finally to kill the patient.

iii. Abnormality of the Coronary Arteries.

The most important single factor in a consid-

eration of myocardial hypoxia is the mechanical diminution of coronary artery capacity brought about by atheroma of the coronary vessels. The incidence of a reduction of coronary luminal capacity by more than half, was found by White, Dry and Edwards (1950), to be seventy-five per cent of men between the ages of fifty and fifty-nine. Among a like number of women, Ackerman, Dry and Edwards (1950), found that the peak incidence was in the decade, seventy to seventy-nine years, and it involved about sixty per cent of patients examined.

Of the cases selected for the "relative myocardial hypoxia" group, forty-three per cent had coronary artery disease which was described at autopsy as gross, fifteen per cent had a moderate degree of atheroma, and in forty-two per cent the coronary vasculature was found to be normal or minimally atheromatous. In the hearts of this group in whom evidence of acute myocardial infarction was seen, fifty-five per cent had gross coronary disease; nineteen per cent had moderate atheroma and twenty-six per cent had normal or minimally atheromatous coronary vasculature. Thus although coronary disease was the most important single factor in the production of myocardial hypoxia in this acute infarction group, about a

quarter of the patients in whom myocardial infarction occurred had no significant disease of the coronary arteries.

Haemorrhage occurring into an intimal plaque of atheroma was considered by Paterson (1936) to be significant and not infrequent. Investigations by Wartman (1938), French and Dock (1944) and Yater (1948) have lent weight to this thesis. However, as Hamilton (1955) points out although the number of times blood is seen in the atheromatous mass within the intima is undoubtedly high, the occasions on which the haemorrhage within the intima is sufficient to occlude or partially occlude a vessel are few. It is doubtful if pressure in the capillaries can ever reach a high enough level to cause an effective eruptive force to blast an atheromatous plaque from its base. There are, however, examples in which a dissecting aneurysm-like phenomenon starting with a small internal tear in relation to a patch of atheroma results in occlusion by an atheromatous mass and perhaps even superimposed thrombosis. The autopsy appearances in a seventy-five

year old female patient of this series (N 3457) were highly suggestive of such a mechanism.

Branwood and Montgomery (1956) concluded from their study that in most cases failure of the coronary circulation was due to lesions in many parts of the vascular tree. The findings in the coronary vasculature of this autopsy series are in agreement with this statement. Further confirmation has recently been published by Crawford and his colleagues (1961), who studied the hearts of seventy-five men who died suddenly from ischaemic heart disease. They state "The frequency with which two or three of the arteries may be occluded or severely stenosed provides a gloomy prospect for coronary artery surgery."

Recent coronary thrombosis was found in eight of the fifteen hearts in which large (i.e. ++ or +++ in table V) acute infarctions primarily of the left ventricle were found. In a further three cases of the fifteen, occlusive coronary disease had been produced by some process other than thrombosis but in the remaining four cases the coronary arteries although narrowed were patent.

Of the four examples of large (i.e. ++ in table V)

primarily right ventricular acute infarction and nine cases of acute microinfarction (i.e. + in table V) of the right or left myocardium, or both, in only one of these hearts was thrombosis of a coronary artery seen.

Thus in this series in about a third of the cases in whom evidence of acute infarction of the myocardium was present, coronary thrombosis had occurred.

In ten other hearts of this series, coronary thrombosis was found. In three cases, the coronary thrombosis was completely or almost completely organised; the hearts of these cases contained healed infarcts. In the other seven cases, recent thrombosis of the coronary arteries was associated with evidence of acute hypoxic degeneration of the myocardium (see page 222). In no case in which coronary thrombosis had recently occurred was there failure to show these acute degenerative changes by staining with the phloxin milling yellow sequence.

Thrombosis occurred only in severely or moderately severely atheromatous arteries. There was no evidence to support the suggestion of Gresham and Howard (1960 a and b) that coronary thrombosis can occur in the absence of atherosclerotic plaques.

The apparently low incidence of coronary thrombosis in relation to acute myocardial infarction in this series is to some extent dependent upon the strict criteria used for the diagnosis of acute infarction (page 168) and the number of microinfarctions revealed by a survey of twenty-five to thirty blocks of each heart.

Systemic disease in which there is a generalised thrombotic tendency will be a factor in the production of myocardial hypoxia to the extent that the risk of thrombosis in the coronary vasculature is increased.

Coronary embolism, in contrast to coronary atherosclerosis or thrombosis, is a rare cause of myocardial infarction. Virchow in 1856, was the first to describe this accident and to trace its source to bacterial endocarditis. Saphir (1933) and Hamman (1941) found dislodgement of bacterial vegetations from the aortic or mitral valve to be responsible for the majority of cases. Other causes are thrombotic or atherosclerotic material becoming impacted in a coronary artery, thrombi covering atherosclerotic plaques at the root of the aorta, intracardiac mural thrombi, thrombi in pulmonary veins and

paradoxical emboli from peripheral veins. To this list have been added emboli of neoplastic origin (Thompson and Evans, 1930) and a unique instance of an embolus originating from a nodular calcified aortic valve free of bacterial endocarditis has been reported (Moragues et al., 1950). Coronary embolism has now been reported following repair of a ventricular septal defect (Winters et al., 1960). Thrombus originated from a repair site and embolism of an otherwise normal anterior descending coronary artery resulted in the production of a subendocardial infarction of the anterior left ventricular wall.

In this series, the only cases in which embolism was considered to have been a factor in the production of relative myocardial hypoxia were the three in which bacterial endocarditis was diagnosed. Widespread micro-infarction and acute degenerative change were seen as were numerous microemboli in the intracardiac coronary vessels. In one case (N 3429) a mass of thrombus was found in the grossly atheromatous left coronary artery and although no bacteria were demonstrable in the thrombus it may well have been of embolic origin.

In a discussion on the significance of lymphocytic infiltration of the adventitia of the coronaries, Gerlis (1956) suggested that "local anoxia occurs in fatal coronary cases as a result of spasm of the vessels, particularly the small vessels of the coronary adventitia." He noted that focal adventitial infiltrations of the coronary arteries occurred in certain examples of "non-coronary death" and stated that they were associated with and, in fact, caused by, a state of anoxia. In the "coronary deaths" on the other hand these adventitial lesions were found in the absence of generalised anoxia. Thus, he argued that if anoxia is responsible for adventitial infiltrations in the non-coronary deaths anoxia must play a local role in the coronary group.

From the statistical analysis of this work it seemed unlikely that adventitial infiltration of the coronary vasculature was related to the degree of atheroma. However, the true incidence of lymphocytic infiltration of the coronary adventitia is extremely difficult to assess unless multiple blocks of the coronary vasculature are taken. Another point is, how many lymphocytes constitute an infiltrate? It is very common

indeed, especially in association with an atheromatous process, to see a few lymphocytes infiltrating the adventitia of the extramyocardial coronaries and occasionally the arteries and arterioles within the myocardium itself. Another factor responsible for much of the lymphocytic infiltration of the main coronary arteries is pericardial abnormality. In the hearts examined, thickened and infiltrated areas of pericardium have frequently been seen in association with, and occasionally without, coronary vascular disease.

The role of coronary spasm in the production of death is extremely difficult to assess and although the clinical effect of vasodilator drugs is very impressive, it is difficult to conceive of spasm occurring in the coronary arteries in which atheroma has not only caused intimal encroachment of the lumen but also secondary destruction of the elastica.

Myocardial necrosis without coronary occlusion has been described in epileptics and it has been suggested that in such cases it is due to spasm of the coronary arteries (Neubürger, 1933).

Angiospasm acting in conjunction with stenosed

intramural arteries has been suggested by Karakasa (1959) as the mechanism of the extensive heart damage which occurs in Kokuzan Disease, so named because of its endemic prevalence in the Kokuzan district of central Manchuria. This is a rapidly fatal condition mainly of girls and young women. Extensive miliary infarcts, focal myocytolysis and fatty change in the myocardium occurs with no evidence of abnormality in the main coronary vessels. The intramural branches of the coronary arteries however are frequently oedematous, sometimes necrotic and thickened intima can reduce the lumenal diameter severely. Similar lesions have been produced experimentally by a number of substances. Histamine liberators and Isoproterenol (Rona et al., 1959) may cause some of their damage by their angiospastic action.

Spasm may well act at arteriolar level but as far as arteries are concerned this theory was well summed up by Allbutt (1915) who said "The truth is that spasm of the coronary arteries is a nasologist's conceit to explain puzzles of his own making."

Inflammatory disease of the coronary vessels is uncommon. In a study of heart lesions in rheumatoid disease by Cruickshank (1958), material from one hundred necropsies of patients suffering from rheumatoid disease

was investigated and "coronary artery disease or its complications were present in thirty-three patients." Active or healed arteritis was found in twenty patients. Occasionally destruction of the vessel wall occurs in the acute lesions of rheumatoid arthritis which have all the characteristics of polyarteritis nodosa.

In polyarteritis nodosa relative myocardial hypoxic lesions are frequently seen (Knowles et al., 1953). Of interest in this group of diseases was a woman of seventy-five years (N 3610) in whom widespread infarction of the myocardium was found in association with a giant cell arteritis of the intracardiac coronary vasculature (figs. 112 and 113). The vasculature was by no means uniformly involved but throughout the myocardial sections, one or two vessels in each showed typical giant cell arteritis. The patient collapsed one morning and died early the next. No evidence of arterial change was seen in any of the other organs examined (liver, spleen, kidney and lung) but the temporal and skin vessels were not examined. At autopsy a pericarditis was noted. The left ventricle was mildly hypertrophied and the myocardium was distinctly mottled

and streaked in the anteroseptal area of the distal third of the left ventricle. I wrote at the time of the autopsy "The appearances are not classically those of a recent infarction. The streaking is somewhat patchy and only punctate areas of necrosis are seen." Mural endocardial thrombus was found in the cavity of the right ventricle near the apex. The right auricular appendage also contained some adherent thrombus. Six centimetres from its origin the anterior descending branch of the left coronary was grossly narrowed whereas elsewhere the coronary vasculature was only mildly atheromatous. These extramyocardial vessels looked atheromatous macroscopically and on microscopy no evidence of inflammation was noted.

The history of this patient is most unusual. She complained of left inframammary pain for eighteen months and stated that the region was tender to touch. She was unable to sleep on her left side because of this pain. She is said to have been "uneo-operative" and her history has obviously been obtained with difficulty. She died the day after admission. From this story it is possible that the coronary arteries were not the only vessels involved by the granulomatous inflammation

although there is no specific retrospective evidence to suggest a temporal arteritis.

Granulomatous or giant cell arteritis was first described by Hutchinson in 1890 (cited by Morrison and Abitbol, 1955). However, only since 1937, the year of publication of a paper by Horton and Magath, has the clinical and pathological entity "temporal arteritis" been split off from the group of generalised angiitides. Temporal arteritis is a disease of the elderly and is more often seen in females than males. Inflammation of the temporal arteries is often accompanied by involvement of the ophthalmic arteries which causes partial or complete loss of vision, the most commonly seen serious complication of this self limiting disease. From the report of Sprague and McKenzie (1940), temporal arteritis may be accompanied by inflammation of almost any artery in the body, the coronaries included. Angina pectoris was noted to accompany a case of temporal arteritis reported by Cole (quoted by Kristensen, 1952). A case report by Cook and his colleagues (1946) showed coronary arteritis without infarction and Kaye (1949) reported seven cases in one of which a pericarditis occurred. This patient

recovered. In 1955 Morrison and Abitbol reported the first case of temporal arteritis in which myocardial infarction occurred in a heart, the mildly atheromatous coronary arteries of which, though patent, were the seat of a giant cell type of inflammation.

It may be that the seventy-five year old woman (N 3610) of the routine autopsy series is another example of this syndrome.

iv. Diseases of Arterioles

Many of the processes which bring about diminution of the luminal diameter of coronary arteries, also act at arteriolar level. Spasm, embolism, thrombosis, and inflammatory disease may all result in arteriolar occlusion.

In addition, however, arteriolosclerosis must be considered as a factor in the production of relative myocardial hypoxia. Medial and intimal thickening of the small radicles of the coronary vasculature is proportional to the degree of hypertension (Kathke, 1955; Linzbach, 1947). Hypertension, however, is one of the factors which determines the development of hypertrophy. Hypertrophy is in itself a major factor in the consideration of relative myocardial hypoxia and thus, it is impossible to

divorce the contribution of arteriolosclerosis from that of hypertension (now to be discussed) to the degree of relative myocardial hypoxia produced.

MYOCARDIAL FACTORS

Hypertension acts directly in the production of myocardial hypoxia by causing medial and intimal thickening of the small radicles of the coronary arteries (Kathke, 1955; Linzbach, 1947), by encouraging atheroma in the coronary arteries themselves (Paterson et al., 1960) and indirectly, by producing hypertrophy of the myocardium, the subject of Chapter Three. Myocardium, hypertrophied for any reason, has a remarkable but ill-understood susceptibility to oxygen lack. It was long thought that this was related to the fibres becoming progressively thicker (Eppinger, 1931), the distance from the capillary to the centre of the fibre becoming too great for efficient diffusion of oxygen. This was stated to account for the heart failure that so often accompanies marked hypertrophy. Büchner (1939) found additional indirect evidence to strengthen this argument. He described the focal necrosis followed by focal and diffuse

fibrosis that is undoubtedly a feature of hypertrophic myocardium. However, it is now well established that in many cases hearts in which the left ventricle is pathologically thickened the capillary-to-fibre ratio is not abnormal and the diffusion distance is not essentially greater than it is in examples of physiological hypertrophy. Therefore, without taking into consideration the factor of capillary length, the explanation for focal hypoxia in hypertrophic myocardium is not to be found in the width of the spaces between the capillaries (Linzbach, 1960).

In addition, according to Schoenmachers (1949) there is a linear relationship between the total heart weight and the diameters of the coronary arteries up to a heart weight of 500 G., so that it would appear that contrary to much of the present-day teaching, the evidence suggesting that the myocardium "grows away from its blood supply" is very sketchy. It may be that the enlarged coronary arteries themselves are more prone to the pathogenetic factors which result in atheromatous change but the ability of the vessels to grow with the heart is striking, and even authors who suggest that splitting of

fibres occurs after a critical heart weight has been reached are convinced that the capillary to fibre ratio constancy is maintained.

A factor which may be implicated in a consideration of the susceptibility of hypertrophic hearts to relative myocardial ischaemia is "functional myocardial stress". This vague term may be more clearly explained by a consideration of the work of Vinogradow (1957).

Infarction was produced in the hearts of rabbits by applying a ligature to the anterior descending coronary artery. In the same animals the pulmonary artery was narrowed to one-third by a constricting ligature. In another series of experiments infarction was produced in animals without constricting the pulmonary arteries. The extent of the infarction in both groups of animals was studied on histotopographic sections made from celloidin and paraffin blocks of the whole organ. By combining a localised circulatory disturbance in the myocardium, with a functional overburdening of the right ventricle, it was possible to obtain regularly an infarction of the anterior wall of the right ventricle. By ligating the pulmonary artery after the infarction had formed, a zone of fresh necrosis developed at its periphery, corresponding

in size to the degree and duration of the hypertension. The conclusion to be drawn from this important paper is that a progression of the myocardial infarction is possible under a combined influence of hypertension in the pulmonary circulation and functional stress of the right ventricle.

The changes of relative myocardial hypoxia were commonly seen in this series in the hearts in which right and or left ventricular hypertrophy had occurred (tables I, II and V).

In thirty-nine of the forty-two hearts in which the combined weight of the left ventricle and septum was greater than 189 G. (table I) lesions of relative myocardial hypoxia were found in the left ventricle. In thirty-one (73.8%) of this group infarctions, acute healing and/or healed (defined on pp.168-9) were found and in fifteen of the forty-two cases (35.5%) acute infarction had occurred with or without evidence of previous myocardial damage.

The two cases in this group in which no myocardial lesion other than hypertrophy was seen were males, aged seventy-six years (N 3443) and forty-six years (N 3468).

The first of this pair was probably a mild hypertensive (he was stated to have a blood pressure of 150/85 mm. Hg. on admission with an extensive pneumonia) in view of the considerable renal vascular disease found on microscopy. His main coronary vasculature however was healthy, and he died from his pneumonia in which abscess formation had occurred. The second patient also had a normal if somewhat heavy heart. However it is in such a case that the boundary between pathological and physiological hypertrophy becomes very difficult to draw. This man was a six foot tall barman, weighing thirteen stone. It was when lifting a heavy crate that his first subarachnoid haemorrhage occurred. He was shocked on admission but made a good recovery (to the hypertensive level of 140/110 mm.Hg.) He was refused neurosurgery because of an alleged abnormality of the electrocardiogram that was recorded in the neurological unit to which he was sent. On his return, the original and other tracings were reviewed and the patient died from a further haemorrhage from a congenital cerebral aneurysm. The opinion of Professor I.G.W.Hill on the electrocardiograms of this unfortunate patient is given with the abstract of his case notes (Appendix A).

This man's heart was fully examined and no evidence of myocardial damage past or present could be demonstrated. I can offer no organic explanation for the electrocardiographic abnormality.

Of the thirty-two hearts in which the right ventricle weighed more than 69 G. twenty-two (71%) showed infarctions and degenerations described later in this chapter as lesions of relative myocardial hypoxia. In eleven of the thirty-two hearts (34.4%) acute healing or healed infarction had occurred and in six hearts (18.7%) evidence of acute infarction only was seen.

Although right ventricular infarction (without infarction of the left ventricle) is rather uncommon and the numbers are small, a very striking feature of difference between infarction in the left ventricle from that of the right emerges. There is a high correlation of left ventricular infarction and coronary disease, whereas in cases in which right ventricular myocardium has been primarily infarcted (that is, not involved secondarily by an extension of left ventricular infarction) this correlation with coronary disease is almost nil. There were only five hearts in the series in which the right ventricle was infarcted without evidence of left ventricular

infarction. In one the coronary arteries were normal, in another minimally atheromatous, and in three moderately atheromatous.

The remarkable incidence of the lesions of relative myocardial hypoxia in the hypertrophic right ventricle was well known to Weinschenk (1939) who stated that in 66% of hearts with right ventricular ischaemia muscle necrosis (which is not present in the left ventricle) occurs. The present series cannot match this figure but the incidence of all the lesions of relative myocardial hypoxia in hypertrophic right ventricular myocardium is striking and it would appear that in the right ventricle, hypertrophy is more important as a factor of hypoxic change than the state of the coronary vasculature. For the left ventricle it is more difficult to assess the relative value of hypertrophy as a factor in the production of relative myocardial hypoxia in view of the complication of the frequent association of hypertrophy and coronary atheroma, and arteriolar disease, a topic already discussed in Chapter Three.

The role of fibrosis as a hypoxia-producing factor is difficult to assess in view of its relation to the other

factors under review. Nevertheless fibrosis can considerably disturb the distribution of the cardiac vasculature, and must play some part in the production of further hypoxia where it assumes a perivascular distribution. Fibrosis may, however, be of the most importance in relation to the compensating hypertrophy that occurs in myocardial cells surrounding and between the bands of collagen.

Myocarditis has been described by Saphir (1959), de la Chapelle and Kossman (1954) and others, as a relatively common complication of the infectious fevers, and they state that in routine post-mortem examinations the incidence of myocardial inflammation (excluding rheumatism and diphtheria) is in the region of ten per cent. In the present series inflammatory disease of the myocardium was seen in eleven hearts of which one was rheumatic, giving an overall percentage of eight.

In five of the ten "myocarditis" hearts, degenerative changes suggestive of relative hypoxia were seen. In one of these five, the case of recrudescent rheumatism (N 3773), gross aortic and mitral stenosis and a moderate degree of tricuspid stenosis had produced a considerable hypertrophy

of the myocardium, and it is debatable whether the rheumatic myocarditis played any significant part in the weighing down of the myocardial side of the relative myocardial hypoxia equation. In three cases of this sub-group of five examples of myocarditis, bronchopneumonia (in two cases probably influenzal and in one case non-specific in a chronic bronchitic) was associated with acute degenerative changes which were focal, and considered of hypoxic rather than viral or bacterial origin. However, this point is disputable. In one of the three cases (N 3393) electrocardiography produced a relative ischaemic pattern of tracing and in all three only the functionally loaded right ventricular myocardium showed evidence of the acute degenerative process whereas both ventricles contained foci of inflammatory cells.

In the heart of the fifth case (N 3403) of this group, a granulomatous myocarditis was found in the hypertrophic already-scarred myocardium. Gross coronary disease was also present. In the anterior mitral papillary muscle, foci of acute infarction were found. This patient had had a leaking duodenal ulcer which had

caused a localised peritonitis and pancreatic fat necrosis. Finally the ulcer perforated and a generalised peritonitis was found at post-mortem examination. The patient was admitted moderately dehydrated and extremely ill and died thirty-six hours later. It must be assumed that the myocarditis was secondary either to the peritonitis or perhaps to the products released by the necrotic process in the pancreas.

It is impossible to estimate the contribution of inflammatory disease of the myocardium to relative myocardial hypoxia in human material in which there are so many other factors at work. Only by studying each in isolation can some assessment of their relative importance be gained. Nevertheless, by the observance of the strictest criteria for the diagnosis of myocarditis (pages 264-268) it has been found that in half of the cases in which this diagnosis has been made, changes of relative myocardial hypoxia have been seen. In addition, in one case of the diphtheria series (page 241) acute infarction was seen in the heart of a child in whom no factors other than those of diphtheria itself were present.

Whether by the local mechanical effects of the

inflammatory reaction or by the associated increase in the metabolic demands made by the inflamed myocardium, myocarditis appears to play a role in the production of relative myocardial hypoxia.

Physical exercise is an obvious factor in a consideration of relative myocardial hypoxia. It is one of which Parry was well aware and on which Burns so interestingly drew a parallel with the muscles of the limbs. It is common clinical knowledge that the performance of physical exercise is a real hazard to the patient with a heart in which a combination of the hypoxic factors under discussion have been active. It is, of course, in relation to this factor that obesity is so important.

Haematological Factors

In the acute phase of shock, the heart exhibits no significant or characteristic pathological changes which may be called distinctive of the shocked state. It is known that the heart is capable of responding to shock with an increase in cardiac output and an elevation of arterial pressure towards normal when fluid replacements are

given by intravenous infusion. However, in the absence of therapy and presence of the shocked state for a critical period of time, the myocardium undergoes hypoxic change of a characteristic type.

The conception that the myocardium remained unaffected by shock was shattered by the work of Wiggers and his colleagues (Wiggers and Werle, 1942; Werle et al., 1942; Wegria et al., 1943) who concluded that myocardial depression may be of considerable importance in the terminal circulatory failure observed in shock. They also stated, as had others, that the depression was in all probability the result of prolonged reduction in coronary artery blood flow with resultant anoxia. The observed changes were given an anatomical basis by Mylon and his co-workers (1944) who described cardiac lesions in dogs surviving tourniquet shock and by Hueper and Ichniowski (1943) in animals killed after recovery from histamine-induced shock. Dogs subjected to prolonged shock induced by a variety of techniques were found by Melcher and Walcott (1951) to have areas of fatty infiltration and necrosis of cardiac muscle when killed after recovering from the shocked state. Anoxaemia was

suggested as the underlying cause.

A not uncommon syndrome of this type is seen following pulmonary embolism, to which attention was drawn by Friedberg and Horn (1939). Myocardial necrosis in such a case is mediated by a hypotension phase (and any of the other hypoxia-producing factors present), to which asphyxia and an exaggerated reflex vagal activity may contribute.

Thus shock may be a factor in the production of acute myocardial hypoxia, but it should not be forgotten that it is an important result of severe hypoxic lesions. The hypotension following an acute infarction of the myocardium will tend to cause extension of the area of hypoxia.

A case in which shock was the cause rather than the result of myocardial infarction, was a fifty-three-year old male (N 3537) in whom haemorrhage occurred from oesophageal varices. The patient was admitted in shock, was transfused and died in hepatic failure four days later. This man never really recovered from his shocked condition and developed an extensive recent infarction in both the right and left ventricular myocardium. His coronary arteries were only moderately atheromatous.

Histologically the age of the hypoxic process was assessed at as little as fourteen hours in some areas and as much as thirty-six hours in others. In the very remarkable incidence of hypoxic myocardial change in cases of influenzal broncho-pneumonia (see pp. 228-230, 282-283) the degree of shock produced is almost certainly a significant factor.

As will be discussed on pages 300-301, shock makes the problem of assessing the effect of noradrenaline on the heart a very difficult one. Noradrenaline is undoubtedly a cardiac toxin capable of producing a focal necrotic myocarditis. However, it is in the very cases in which noradrenaline is given that the focal hypoxic necrosis of shock (and polymorph infiltration) is most likely to occur.

In spite of what has been said about the role of shock in the production of myocardial ischaemia, it should be noted that there are E.C.G. changes which may be obvious following the taking of as little as 450 ccs. of blood (Scherf and Klotz, 1944). In this paper changes in the E.C.G. pattern were reported in the absence of shock, without severe anaemia and independent of the haemoglobin level.

In a recent paper reporting three cases in whom myocardial infarction followed acute gastro-intestinal haemorrhage, Davison and Smith (1960) concluded that post-haemorrhagic cardiac disturbances are due to an inadequate coronary blood flow secondary to the reduced circulating blood volume. The importance of early restoration of blood volume after haemorrhage, especially in the elderly, was stressed.

Even in the absence of coronary atheroma a serious degree of anaemia can result in myocardial infarction (Opitz, 1935). In a fifty-four year old woman (N 3406) a gross anaemia (3.8 G. Hb./100 ml.) was secondary to an aleukaemic leukaemia, and contributed to the production of left ventricular and mitral papillary musculature focal infarction. The myocardium was not hypertrophied and the coronary vasculature was normal. In another case of leukaemia (N 3631) acute myocardial infarction was seen, although the coronary vasculature was normal and there was no evidence of thrombosis, leucocytic sludging or embolism in the small vessels of the heart in which much leukaemic infiltration had, however, occurred.

Although by no means all the patients had had their

haemoglobin levels estimated, from the figures available twenty-nine per cent of the "relative myocardial hypoxia" group were anaemic to the extent that they had less than 12 G haemoglobin per 100 ml. of blood, whereas in the normal group only fifteen per cent were anaemic to this level and below.

Anaemia may well be another significant factor in the production of infarction in association with influenzal broncho-pneumonia. The intense haemorrhagic reaction must result in the loss of a significant amount of blood and consequently a diminished oxygen carrying power. Yet another factor in this disease is, of course, the diminished oxygen diffusing capacity of the diseased lung. There is a high incidence of broncho-pneumonia in the "relative myocardial hypoxia" group, but once again it is often difficult to decide whether it is a causal factor or a result of myocardial ischaemia.

Viscosity is a fundamental property of blood that has a direct influence on its rate of flow. The viscosity varies mainly with the cell-plasma ratio and plasma-protein content. Viscosity of whole blood is dependent on the number of erythrocytes and increases with the haematocrit but at a faster rate (du Pré, Denning and Watson,

1906). At the same haematocrit, the viscosity is said to be proportional to the viscosity of the plasma (Trevan, 1918).

The viscosity of plasma is largely influenced by its protein content but variation of fibrinogen has relatively greater effects than albumen or globulin. Myocardial infarction is followed by an increase in the fibrinogen content of the blood, the increase being shown by Gilchrist and Tulloch (1952) to be roughly proportional to the severity of the infarction. Globulin (Dodzelot et al., 1954) and serum mucoprotein (Simkin et al., 1949) levels have also been shown to increase following myocardial infarction. Thus, an increase in plasma viscosity will occur following myocardial infarction which will cause an increase in blood viscosity and further compromise the impaired circulation. This has been proved experimentally by Kellogg and Goodman (1960) who were able to correlate the increase in viscosity of the serum with the increase in fibrinogen level. They found that the viscosity of whole blood rose significantly despite a tendency for the haematocrit to fall.

The interdependence of the heart and lungs is implied in the term "cardiopulmonary disease" (Liebow, 1960). Inadequate oxygenation of blood in the lungs may result from the passage of blood through altered pulmonary substance, through poorly ventilated lung tissue or through a normal piece of lung at too great a speed. Chronic anoxia will lead to hypervolaemia and polycythaemia with an increased blood viscosity, increased tendency to thrombosis and an increased cardiac output. Hypoxia has been shown to result in cardiac enlargement (Barnard, 1958; Norman and Coers, 1960), with all the hazards this change involves.

In more than half of the cases of this "relative myocardial hypoxia" group of cases, pneumonia has been present at death. A striking example was that of a seventy-year old male (N 3737) in whom a lobar pneumonia treated at home failed to resolve and twenty-four hours before death he was seized with pain in the chest. At autopsy, failure of resolution of a lobar pneumonia was found together with a left ventricular acute myocardial infarction aged, histologically, twenty-four to thirty hours. Gross coronary atheroma had not been of sufficient intensity to cause the infarction during the acute phase

of lobar pneumonia. However, during this infection, the myocardium no doubt ran up an oxygen debt, the speedy repayment of which was made impossible by failure of resolution. Respiratory disease is thus not only important as a factor in the production of right-sided myocardial hypertrophy but the associated central hypoxia can be critical.

However, it must not be assumed that it is possible to determine the relation of heart disease to acute inflammatory disease of the lung in every case. Broncho-pneumonia may occur as a result rather than as a cause of heart disease but may then act causally in worsening the myocardial state.

Disseminated necrosis of the hearts of animals poisoned by carbon monoxide was reported by Herzog (1919), Christ (1934) and Kroetz (1936). Cases of gas poisoning in humans have been reported and multiple, mainly subendocardial foci of myocardial necrosis, have been found; Neubuerger and Clarke (1945) pointed out that in some instances they appear some time after the inhalation of the gas.

Summary

In the evolution of relative myocardial hypoxia, the mechanical coronary factors are by far the most important, but haematological and myocardial factors make significant contributions to the production of hypoxia, the absolute degree of which is not nearly as important as its value in relation to the myocardium.

The Histological Diagnosis of Relative Myocardial Hypoxia

Cardiac infarction is the extreme of a continuum of graded hypoxic injuries affecting the metabolic integrity of myocardial cells.

Dorland rather inadequately defines an infarct as an area of coagulation necrosis in a tissue, due to local anaemia resulting from obstruction of circulation to the area. The abundance of red cells within a zone of infarction disqualifies the use of the term local anaemia. Hypoxia is the factor of importance. Within the myocardium the local hypoxia, as has been discussed, may result from many more causes than obstruction of circulation to the area. Dorland's definition when applied to the myocardium also ignores the practical histological difficulty of assessing the significance of an area of abnormality which on routine staining is characterised by "glassy eosinophilia". Even in cases with a classical history, a known time interval between the onset of symptoms and death, and a brief interval between death and autopsy, the early glassy eosinophilic change so glibly described in the textbooks as typical of early infarction, may be

extremely difficult to distinguish from the artefactual eosinophilia to which tissues may be prey as a result of inadequacies in the techniques of fixation, dehydration, staining and mounting. Corroborative polymorph leucocytic pavementing or better still, infiltration and the early lysis of nucleoprotein, are histological features which can resolve the doubts of the pathologist in the diagnosis of myocardial infarction.

For the purpose of this study, I have accepted this rather restricted histological definition of the term acute infarct. If as a result of the interaction of coronary, haematological and myocardial factors, a local hypoxia results in a coagulation necrosis of sufficient severity to elicit a neutrophil polymorph response, that area in which necrosis has occurred is said to be <u>acutely infarcted</u>. This definition precludes a histological diagnosis of infarction until eighteen to twenty hours after the onset of the local hypoxia, and restricts the term to a time limit of some eight to ten days by which time the neutrophil polymorph exudate has been largely replaced. The presence of macrophages, lymphocytes and plasma cells, and early collagenisation of the area are the features of a <u>healing infarct</u>, the elements of which

are well established by the second week.

The third stage of the process, a firm scar, is established at a time which varies with the size of the area involved. However, on average by about six weeks after acute infarction has taken place, a mass of collagen of variable vascularity replaces the destroyed muscle and such a lesion is defined as a healed infarct. The true healed infarct must show evidence of collagenisation of myocardial cells and must not be confused with interstitial or reticular fibrosis which follows inflammation and hypertrophy of the myocardium.

The recognition of "early myocardial infarction" has occupied the minds of many able workers over the years and energetic attempts have been made to reduce in the autopsy files, the number of cases in which coronary thrombosis has resulted in the speedy death of a patient in whom "no message is written on the heart." Histochemistry has revealed changes in the hearts of animals in which ligation of a coronary artery has been followed by detectable change in the ischaemic myocardium in as short a time as half an hour (Kent and Diseker, 1955). By many authors, and in Experiment H (page 375) electron

microscopy has been shown to reveal mitochondrial changes within twenty minutes of the induction of hypoxia. Experimental work, however, is of limited application to human tissue obtained at autopsy and although some of these histochemical methods have undoubtedly been proved of great value, it must be borne in mind that the changes that are revealed do not indicate early infarction, but early degeneration which may or may not lead on to cell death.

The inference that an area of the myocardium in which early histochemical or mitochondrial structural changes are seen, will run the course of an infarction may be true, but it also may be false. The acute changes of a hypoxic phase may be followed by one of a series of histological patterns. There is a varying response of individual myocardial cells to a given degree of hypoxia, and there is a gradation of response which occurs with a steadily increasing oxygen level, as the centre of the infarct is left behind. At worst, the myocardial cells and a limited amount of stroma may die. Having elicited a neutrophil response and macrophage reaction, the necrotic area or <u>infarction</u> becomes organised.

Alternatively, a few myocardial cells may die without stromal death, to produce the histological picture of focal myocytolysis. Thirdly, the cells in which early histochemical abnormality is demonstrable after hypoxia, may not be sufficiently damaged to cause their death but may be metabolically unable to fulfil their role in the use of their many substrates. For example, glycogen or fat may accumulate in the cell to produce such recognisable histological patterns as "glycogenic degeneration" or "fatty degeneration" of the myocardium, lesions of lesser injury than is capable of causing cellular death.

Whereas the morphological pattern of a degeneration of metabolic dysfunction develops by a steady accumulation within the cell of substances like glycogen and fat over a period of days, and perhaps weeks and months, the degenerative process preceding cell death in an infarction or focal myocytolytic lesion occurs in a matter of hours. It is an acute degeneration characterised by irreversible alteration to the myofibrillar arrangement, and is a change which may be brought about not only by severe hypoxia. Cell necrosis is the inevitable consequence of an acute degeneration but as a description

of this process the term "myocardial necrosis" suggests that the cells are already dead. The morphological appearances of this process are not those of dead cells but of dying cells and thus "necrosing myocardial degeneration" is a preferable term although "acute degeneration" seems to be accurate and acceptable. The aetiological agency when known, can be added as an epithet, as for example, acute hypoxic degeneration, acute diphtheritic degeneration, and so on.

Myocardial Infarction

Using the criteria detailed on page 168 , of the one hundred and twenty-five subjects of the routine autopsy series, acute healing or healed myocardial infarctions were found in the hearts of forty-seven patients. The comparison of these and the hearts of the "normal" group (table III) was undertaken to study the full gamut of histological change which could be ascribed to varying grades of local hypoxia.

Table V includes the cases in which myocardial infarctions were found. In the column headed "Fibrosis" (subdivided for left and right ventricles) the estimation of

the degree of fibrosis is attempted. Three pluses in this column signify the macroscopic fibrosis of a healed infarction; two pluses also signify a healed infarction which was not of sufficient extent, however, to be seen macroscopically. On plus in this column signifies reticular or trabecular fibrosis, not associated with previous infarction.

Acute infarction which is extensive is credited with three pluses. The smaller infarcts are given two pluses and the focal infarcts are signified by one plus.

In thirty-six (76.5%) of forty-seven infarcted hearts healed infarction was present, and in twenty-one (58.3%) of these thirty-six hearts, acute infarction was also seen.

The distribution of the acute infarctions is of interest. Of the twenty-eight hearts in which acute infarction was seen, in twenty-four the left ventricle (including septum) was primarily involved, the right ventricle also showing areas of infarction in nine (31.9%) of these. In the other four of this acute infarction group the right ventricle was solely or primarily involved.

Acute Infarction

One of the striking histological features of myocardial infarction is the very remarkable variation in effect a given degree of hypoxia has on the constituent tissues of the heart. The myocardium is relatively easily damaged by a reduction in local oxygen tension whereas stromal tissues are capable of withstanding a severe hypoxic episode. However, also of considerable importance is the extent to which myocardial cells vary from one to another in their response to a given degree of oxygen lack. In much the same way as liver parenchymal cells vary in their response to a toxin according to their glycogen content, and so on, it appears that some myocardial cells may be able to withstand a degree of hypoxia which their neighbours are unable to survive. This may be due to a variation in their cell content or their state of metabolic activity. The functional load to which an area of myocardium is subjected in its work may also be a factor in the microscopic localisation of the degenerative changes occurring within the area of local hypoxia. In muscle generally it is considered that groups of fibres take turns in periods of activity and in the heart this may also occur. Probably

a combination of these reasons accounts for the fact that in an area of infarction, certain fibres or even groups of fibres are spared the necrosis which afflicts their neighbours. Others may be seen in which the injury which has occurred is of lesser degree than complete necrosis. Indeed in an area of infarction, say forty-eight hours old, the changes by which the process is aged histologically, are accompanied by earlier changes in some muscle bundles which have succumbed at a later date. This may be contributed to by a further compromise of the circulation in the myocardium resulting from shock, and the serial rise in blood viscosity (Kellogg and Goodman, 1960) which is associated with the rise in fibrinogen levels shown by Gilchrist and Tulloch (1952) to take place after myocardial infarction. The whole play must be visible from start to finish although it is by a consideration of the last act that the length of the performance is estimated. It is by studying infarcts of this type that some assessment of the ways in which pathological changes develop in the myocardium subjected to this hypoxic type of injury may be made. The normal myocardial fibres when stained with phloxin followed by milling yellow differentiation, show the fibrillar pattern running the length of the myocardial cells (figs. 4 and 5)

the cells themselves being bounded by intercalated discs, and sarcolemma, at each end and peripherally (figs. 5 and 6). The discs and fibrils are phloxinophil and the distinct banded structure is demonstrable in the myocardium (fig. 7). The dark anisotropic zones (with their central Z bands) alternate with lighter isotropic zones (in which the central bands are designated by the letter H).

The first stage of the infarction process is one of acute hypoxic degeneration leading to necrosis of many cells within an area of myocardium. Coagulation necrosis of the proteinous material of which the fibres are made up, is followed by shredding of this material into relatively large hyaline fragments which align themselves roughly across the breadth of the fibre (figs. 11 and 15, 141, 159-163). Between these "coagulation bands" there is a dusting of the cells by granular phloxinophilic coagulation dibris. This process of coagulation is followed speedily by lysis (figs. 116-117). In the areas in which leucocytic infiltration has taken place the amount of lysis is considerable (figs. 17 and 19) and there may be only thin coagulation bands ranged across the fibres whereas in areas showing more recent degenerative change or where there is less leucocyte infiltration the coagulation bands and inter-band granulat-

ion are very much more extensive. Polymorphnuclear leucocytes contribute a high level of lytic activity to the area, although on purely morphological grounds it is apparent that proteolysis can proceed, if only relatively slowly, before the arrival of, or even in the absence of polymorph leucocytes.

The polymorphnuclear leucocytic infiltration in acute infarction is elicited by the leucotaxic influence of necrotic myocardium, the death of the tissue being brought about by its acute degeneration in response to a critical level of relative hypoxia. As was stated by Mallory and his colleagues (1939), in a given area of infarction the infiltration starts peripherally and spreads centrally, being more active on the epicardial than the endocardial side. There follows a progressive increase in polymorph leucocytes over the next four days or so but after about forty-eight hours, these early invaders begin to break down, a feature which coincides with a progressive increase of basophilic nuclear debris which is maximal at about the end of the first week.

It has been noted by Barrie and Urback (1957) that "neutrophils make a curious reappearance in the centre of the infarct at ten days". It may well be that this occurs

as a result of the re-establishment of the circulation with fresh blood and neutrophils finding their way into the vessels of the infarcted area, but another reason may be that the leukotaxic effect of the more resistant myocardial cells that have undergone secondary or delayed necrosis has induced a second wave of leucocytic response from the vascular zone of absorption. It is in addition more commonly seen that a later leucocytic response occurs in peripheral zones where it seems likely that secondary circulatory disturbances, and the oedema and exudate of infarction have inflicted local vascular damage, in turn causing an extension of the area of critical hypoxia which is able to bring about the necrosis of more myocardium.

The absence of nuclei is usually a feature of the hypoxic myocardium by the time polymorphnuclear infiltration is apparent. Nucleolysis occurs without pyknosis.

The prominence of the A and I zones is often very noticeable along fibres in and around infarcts and there is an apparent increase in sarcomere length (figs. 114 - 115). There is no doubt that intramyocardial oedema develops early in acutely degenerating muscles. Many

authors have demonstrated its existence either by physical or histological methods (Karsner and Dwyer, 1916; Hermann and Decherd, 1935; Tennant et al., 1936; Büchner, 1939; Lowry et al, 1942; Yokoyama et al., 1955; Martins de Oliveira and Levy, 1960). The mechanism by which this increase in fluid content develops is something of a mystery but most authors consider that the increase in water takes place in the extra-cellular spaces, although intra-cellular swellings may also occur (Caulfield and Klionsky, 1959). Martins de Oliveira discussed the role of interstitial oedema in the physiopathology of acute myocardial infarction and by the use of intravenous hyaluronidase managed to cause rediffusion of this increased water content of infarcted muscle (Martins de Oliveira et al., 1959 and 1960).

Hypoxia far short of the degree necessary to cause frank infarction can produce an increase in water content of the myocardium. Lymph flow from the heart has been studied extensively by Drinker (1942). He states that the flow of lymph from the heart is constant unless cardiac activity is disturbed. By increasing cardiac inflow and output, the lymph flow rises immediately. He quotes Maurer (1940-41) who showed that if the oxygen tension of

the blood is reduced to 75% saturation, lymph production rises. A gross elevation of the amount of lymph flowing from the heart occurs when the blood is only 50% saturated.

It seems highly likely that the pushing apart of Z bands occurs when a steady increase in muscle cell water content takes place but a very early change which occurs, probably immediately following the inflow of hypotonic fluids, is mitochondrial swelling. Indeed, there are those who would say that mitochondrial damage is the primary cause of an increase in water content, the water inflow causing further mitochondrial damage and so on. Ultrastructural studies have shown that the swelling of the mitochondria and endoplasmic reticulum occurs early (figs. 75-78) and is a prominent morphological abnormality (Bryant, Thomas and O'Neal, 1958; Caulfield and Klionsky, 1959). Post-mortem autolysis is characterised by great uniformity of damage and slower development of structural change than in hypoxia but the two processes are essentially similar and probably they depend largely on the same set of enzymes. "Cloudy swelling", "parenchymatous degeneration" or "hydropic degeneration" are the light microscopical terms used for these mitochondrial and endoplasmic

reticulum changes which lose much of their significance in autopsy material.

The term "hydropic degeneration" has been a source of considerable confusion in descriptions of non-specific myocardial changes occurring in heart failure. The "moth-eaten" appearance of the myocardium in which no loss of fibrils is demonstrable and cross striations are seen, is better served by the term "intracellular oedema" whereas "hydropic degeneration" describes a histological pattern in which there is vacuolation of the muscle fibres with droplet formation, the vacuoles not reacting to stains for fat and glycogen (Higginson et al., 1952). This is a commonly encountered change in hearts in which there is demonstrable infarction and in some in which although no actual infarction has occurred, there is evidence of a relative myocardial hypoxia.

Coagulation necrosis is not the only way in which a myocardial cell reacts to a severe degree of hypoxia. Occasional cells appear to undergo what can only be described as an acute oedema (fig. 14). The cell becomes bloated and is apparently then subjected to a direct lytic change of the fibres. The ballooning of the cell may become very

pronounced and only in the region of the intercalated disc is the fibre breadth maintained, giving the fibre the appearance of having a series of constrictions. Occasional cells may be relatively spared or not yet fully involved as, within the fibre chain of cells, occasional areas of typical banding may be pronounced (also seen in fig. 14) suggesting that the degree of water intake has reached only moderate proportions.

In cells showing this acute oedematous change myofibrils are only weakly stainable with phloxin and for the most part the only phloxinophil material is rather granular and amorphous and is scanty in amount. It must be admitted that the acute oedema process may result in an alteration in the affinity of the muscle protein to take up the phloxin stain, but it would appear that what has happened is that the component fibrils have partly dissolved out. Following this acute oedematous process in which lysis occurs, the cell wall may burst, or it may remain intact giving the appearance of a sarcolemmal bound empty space. The fact that the sarcolemmal layers are kept apart (fig. 118) suggests that in fact there remains within the cell a fluid component. Often this is further substantiated by the presence of lipofuchsin granules which

appear to be suspended in these fluid-filled spaces.

There seems no doubt that intracellular fibrillolysis (and nucleolysis) can occur. Such a process is of course autolysis, a much more leisurely process than that incurred by the ferments released from polymorphnuclear leucocytes. Having become necrotic the cell has the ability to cleanse itself of the now useless material with which it is cluttered. The more adequately this can be done, the more likely it is that the "cell", now merely a space - probably fluid filled - bounded by a membrane which formed the outer half of the sarcolemma, can become replaced by the growth of adjacent cells in the same fibre, provided no stromal damage has been inflicted.

It has already been noted that the constituent tissues of the myocardium have differing oxygen requirements and therefore, differing susceptibility to hypoxic injury. Even in severely hypoxic muscle there seems little likelihood that a lack of oxygen of itself will bring about the extensive destruction of reticulin or collagen. Indeed when reticulin preparations of an area of acute degeneration are studied the degree of normality of the reticulin structure is quite striking. The way in which an area of

coagulation necrosis and extensive areas of acute hypoxic degeneration can be spotted in these preparations is that on low power microscopy the meshwork is somewhat more condensed than in normal myocardium (figs. 120 and 121, 147 and 148). These areas appear to have shrunk. This shrunken appearance is not of course seen in relation to the few fibres which show oedematous lytic change without coagulation. In relation to these fibres the reticulin is distended and in places shows a breakdown which appears to be related to a bursting of the oedematous cell itself. This, however, is an uncommon feature.

It is in relation to the polymorph leucocytes that most reticulin damage takes place (figs. 118 and 119). These leucocytes contain strong proteolytic enzymes, the origin of the heterolytic process which acts apparently extracellularly, or upon the very walls of the cells themselves. There is little doubt that leucocytes are the key to the very different end results of hypoxic lesions. Reticulin damage is of paramount importance to the future of the myocardium and it is the extent to which this framework of the heart is involved that will determine the type of repair carried out by the mesenchyme

Leucocytic or heterolytic, and intracellular or autolytic ferments digest necrotic muscle substance for absorp-

tion or phagocytosis by the macrophages. The scavenging process starts on about the fourth day at the periphery of the infarct and disposes of the fragmented and partly lysed muscle debris. When muscle fibres are still enclosed individually by the reticulin fibres of the proto- and perimembranes, or are wrapped in bundles by collagen fibrils, the access of macrophages is uneven. However, the way is laid open by one of three mechanisms. The autolytic enzyme activity within the cell, a rise in intracellular pressure and heterolytic enzymes from the proteolytic leucocytes combine in infarcted muscle to allow ingress of macrophages which, having achieved an entrance to the fibre, ream out the space causing no further damage to the sarcolemmal sheath.

The macrophages usually contain pigment granules. By far the most common pigment constituent of these granular histiocytes is lipofuchsin but it is unusual to be unable to demonstrate some haemosiderin within them. Macrophages may be seen in healed infarcts anything up to two years after the severe local hypoxia occurred.

The Healing Infarct

The zone of absorption in which the macrophages are seen in the periphery of the infarct, is of immense interest histologically. It is from here, according to the textbooks' descriptions, that granulation tissue is seen to grow into the area of infarction to bring about its organisation. According to the classical descriptions of Mallory and his colleagues (1939) and others, newly formed capillaries can be seen to bud off and grow into the infarcted area from about the fourth day. Accompanying these capillaries, fibroblasts showing mitotic figures are described. A most interesting feature which is inadequately stressed in these descriptions is that fibrin is usually a notable absentee from the exudate formed after cardiac infarction. Only rarely do haemorrhages occur within an infarcted area, and I would suggest that only in these rare instances does organisation follow the ingrowth of granulation tissue in the way described.

It was Barrie and Urback (1957) who first questioned this classical theory by stating that following the evacuation of the sarcolemmal sheaths by macrophage activity, the collapsed empty sheath became part of the zone of

absorption. They concluded that the "endomysial" tubes are themselves the "scar" of the infarcted area and that when absorption is complete, the infarct is represented by the blood vessels, and condensed and recolonised endomysium of the original muscle without new fibrous tissue formation.

There seems no doubt that following macrophage activity in relation to the necrotic muscle fibres, reticulin preparations show that sarcolemmal sheath collapse and a concertina-ing of reticulin layers result in the production of a substance of the wavy banded structure of collagen (fig.122). This is confirmed by its marked fuchsinophilia demonstrable with van Gieson staining. This primary "collagenisation" occurs as the absorption zone advances. This zone is characterised by many capillaries full of blood and lined by endothelial cells. The intact myocardium is very richly endowed with capillaries and it seems apparent from the study of reticulin preparations that the endothelial cells grow along pre-existing old capillary channels. The remarkable vascularity of the absorption zone maintains macrophage activity and may also provide the stimulus for mitosis of resting mesenchyme tissue cells, the increase in their number being followed by

fibrogenesis which "weaves the weft" into the collapsed reticulin "warp".

With the introduction of the word "reticulin" into this discussion a definition of what is meant by the term is necessary. Reticulin consists of fine (1μ) isotropic fibres which show true branching and enclose the fibres and vessels of the myocardium in a sheath-like framework (fig. 123). It stains only faintly with acid fuchsin (van Gieson's stain) and appears black in both toned and untoned sections impregnated with silver by the method of Slidders et al. (1958). It must be emphasised however that there are probably different varieties of reticulin and the term as used here is necessarily a wide and imprecise one. In areas of reparative fibrogenesis (for example in the organisation of a thrombus - fig. 124) the immature argyrophil fibres are almost certainly precursors of mature collagen and it may be that as defined here, the reticulin of the normal myocardium under certain conditions can similarly form the basis of collagen fibres. Although collagen is thick, brown and usually distinctly wavy on impregnation with silver it can be extremely difficult to differentiate from reticulin. Indeed, in hypertrophic myocardium, the differentiation by any staining method may be impossible.

The process of organisation to produce a healed infarct is thus fundamentally unlike that of classical description such as is seen for example in the organisation of endocardial thrombus in which the budding and ingrowth of capillaries and the ingress of fibroblasts occurs along the haphazard pattern of the fibrin meshwork (fig. 124). Collagen is deposited in short strands which course in all directions and in all planes to produce tough scar tissue. In the myocardial infarct, however, there is first a reorganisation of a pre-existing scaffolding followed by secondary fibrosis to form what is anatomically a very good but functionally poor imitation of what existed before. The materials for the repair are on the site. Nothing need "grow into" the area (other than endothelium) and the result is an ordered, architecturally sound "layering" of collagenous material (fig. 127), a process which is quite unlike that seen in the haphazard collagen fibre complex of an organising mural thrombus.

FOCAL MYOCYTOLYSIS

A feature commonly seen in the myocardium around infarcts or in hypertrophic myocardium was described by Marie in 1896 as "etat alveolaire". This change has recently been reviewed by Schlesinger and Reiner (1955) under the title "Focal Myocytolysis of the Heart". They stated that the lesions of focal myocytolysis consist of circumscribed areas in the myocardium, up to about 1,500 μ in diameter, in which lysis of the muscle fibres occurs with the production of an open-work pattern of empty sarcolemmal sheaths which gradually collapses and condenses to leave a small scar. Essential features of the lesion are an absence of leucocytic response and the preservation of an intact stroma in the presence of acute lytic changes affecting the muscle cell.

An analysis of the routine autopsy series revealed that in 34.7% of the hearts examined focal myocytolysis was found in the ventricular myocardium. These cases are included in table V, the extent of this change in each ventricle being represented by one to three pluses.

In fifteen of these cases the lesions were found exclusively in the left ventricle and in four they were

present only in the right ventricular myocardium, the remaining eight cases showing focal myocytolysis in both right and left ventricles.

Left Ventricular Focal Myocytolysis

Of the thirty-three cases in whom left ventricular focal myocytolysis was present, in twenty of these the patients had hearts in which the left ventricle was hypertrophied. Of the entire autopsy series, forty-two examples of left ventricular hypertrophy were found so that in 47.5% of these focal myocytolysis was also present.

In twenty-four (73%) of the thirty-three cases in which focal myocytolysis was present in the left ventricle there was also evidence of acute, healing or healed infarction (as defined on pp. 168-169).

In only five cases was left ventricular focal myocytolysis seen in the absence of infarction or hypertrophy of the left ventricle. The first of these was a woman aged eighty-five (N 3427) who was anaemic (10.5 G/100 ml.) and was admitted following haemorrhage into the cerebral glioma. She lived for three days in deepening coma before death. The second was a woman aged seventy-five (N 3455) who had widespread lymphosarcoma which had infiltrated her

heart. The cytolysis was extensive in relation to the infiltration but additional factors in its production were gross coronary atheroma, coronary thrombosis and a marked anaemia. The third of this group of five cases was a woman aged seventy-six (N 3600) who had pernicious anaemia (Hb. 4.16 G/100 ml.) and who died in congestive failure. The fourth case was a man aged seventy-six (N 3752) who died of a broncho-pneumonia. The right ventricle was hypertrophied (and contained foci of myocytolysis) and was infarcted. The last of these five cases was a seventy-four-year old female (N 3790), admitted in congestive cardiac failure. She was hypertensive and died of a lobar pneumonia.

Thus in no case in which focal myocytolytic lesions were found in the left ventricular myocardium, was there a lack of correlation with relative myocardial hypoxic factors. In three quarters of the cases of focal myocytolysis there was evidence of infarction (old or recent) and in nearly half of the cases with left ventricular hypertrophy focal myocytolysis was also seen. In the remaining five cases there was clinical and pathological evidence to suggest that focal myocytolysis had been

produced by relative myocardial hypoxia.

Right Ventricular Focal Myocytolysis

Of the twenty-two cases in whom focal myocytolysis was seen in the right ventricle, ten of these occurred in hypertrophic myocardium. Of the entire series thirty-two examples of right ventricular hypertrophy were found so that in 31.2% of these, focal myocytolysis was found.

In all three cases of bacterial endocarditis right ventricular focal myocytolysis was found and in four other cases in which focal myocytolysis had occurred, acute myocardial infarction had also taken place in the right ventricle.

In three of the four hearts in which only right ventricular myocytolysis was present, the myocardium was hypertrophied (in association with emphysema in one case and mitral stenosis in the other two). The fourth example of the right ventricle only being affected was one of secondary myocardial carcinoma (N 3533) which affected the right ventricular myocardium only. It seems likely that local vascular damage inflicted by the carcinoma led to a degree of relative hypoxia sufficient to produce

focal myocytolysis in the right ventricular myocardium.

General Morphological Features

Initially attempts were made to grade the lesions by size and stage of development. However, nothing short of serial sectioning was found to give valid answers to these estimations and the immensity of the task necessitated its abandonment.

Focal myocytolysis was most commonly seen in the inner third of the myocardium and papillary musculature of the ventricles. In figs. 36 to 39 a longitudinal section of a large area of myocytolysis in the anterior tricuspid papillary muscle is shown. From two central cores of acute hypoxic myocardial degeneration the lesion can be traced distally along the papillary muscle to a single thicker core of degeneration which leads finally to an area of myocytolysis in which the open meshwork of sarcolemmal tubes is still apparent. A small and commonly seen pattern of myocytolysis is seen in fig. 40 (compare fig. 155) in which some of the peripheral fibres appear to be undergoing degeneration. Typical larger and later stages of the lesion are shown in figs. 41, 42, 153 and 154. The sections stained "elastica - van Gieson" shows the intense

fuchsinophilia of the concertina-ing, condensing reticulin, and there is still evidence of non-contracted sarcolemmal sheaths. The adjacent section is impregnated with silver and shows the difficulty in reticulin-collagen differentiation. These photographs show the common site of these lesions in the subendocardial zone of papillary muscles or trabeculae carneae (figs. 44 and 45).

The site of these lesions varies enormously. They appear to be finger-like in shape. As can be seen in figs. 36-39, the whole lesion may extend for some distance through the myocardium with a relatively small cross section.

It must be emphasised that focal myocytolysis is quite distinct from an absorption zone at the periphery of, but continuous with, an infarct in the stage of healing. Much of the description in the literature and even some of the discussion on localisation of focal myocytolysis in the heart in Schlesinger and Roiner's paper, suggest that when myocytolysis is seen in relation to areas of infarction, the differentiation between focal myocytolysis and the lytic absorption zone is no longer maintained. The focal nature of the one process and

the cellularity of the other are points of differentiation which should make for little confusion between the two, although occasionally serial sectioning may be required for their distinction.

Discussion

These miliary lesions were considered by Schlesinger and Reiner to be indicative of myocardial damage caused by a variety of agents. They regarded the process sui generis as one of myocytolysis and a lesion different from the miliary infarct. "In this form of myolysis"(as distinct from that of an infarct), "the muscle fibres disintegrate within a small and discrete territory. Their myofibrils seem simply to disappear. The muscle nuclei of the affected fibres do not undergo rhexis, lysis or pyknosis, but remain visible for some time. At most there is some nucleoplasmic clumping. The sarcolemma is preserved but it collapses ..... No reactive exudation of polymorph leucocytes is elicited ..... At the periphery other muscle fibres disintegrate similarly. This feature gives the process, in contrast to the centripetal nature of smaller and larger infarcts, a centrifugal character ... Eventually all that remains is a small focus of empty but

intact cardiac stroma in the meshes of which are mononuclear cells more or less laden with a finely granular, light brown pigment." (Schlesinger and Reiner).

In what way does this lesion really differ from an infarction? Their similarities are much more striking than their differences. Acute hypoxic degeneration preludes both processes. In some cells, coagulation of the muscle protein is followed by the coagulation, shredding, granulation and band formation that are seen in acute infarction. In other cells, acute oedema occurs with direct proteolysis apparently without preliminary coagulation. In either case, autolysis and absorption cleanse the fibre of the dead tissue, and healing takes place.

The various authors who have described focal myocytolysis (Smith, 1904; Brown et al., 1951; Schlesinger and Reiner, 1955) are satisfied that it is irreversible. There is certainly no evidence to support a theory that the heart cells regenerate as do the liver parenchymal cells after a process similar to focal cytolysis such as occurs in an acute infectious hepatitis. However, myocardial cells can grow by the addition of sarcomeres. It

is possible that if the factors causing the hypoxia are removed to provide oxygenation of the growing cells, and provided the sarcolemmal sheaths are intact, adjacent cell growth could if not wholly, at least partially, re-occupy lengths of fibre in which autolysis of dead cells has left empty spaces. It is suggested (pages 254-256) that such a mechanism spares most diphtheritic hearts of post-necrotic scarring and provided there is no reticulin damage or collapse, such a mechanism may play a part in the reversal of focal myocytolytic lesions. If the gaps caused by cytolysis are too large or if sarcolemmal sheaths have undergone damage, the concertina-ing of reticulin exactly similar to that seen in the healing infarct will occur with the production of focal scarring.

The reason for the absence of polymorph leucocytes from foci of myocytolysis must be considered. One possibility is that the collateral vasculature allows ingress of other blood cells to an area of infarction, but in myocytolysis, a true ischaemic necrosis occurs. This is unlikely. If it were so the area of myocytolysis would be a more profoundly hypoxic looking lesion than the infarct and this is manifestly untrue. These myocytolytic lesions are distributed around infarcts, in the

subendocardium and sometimes para-vascularly so that it would appear that they occur in areas of less intense hypoxia than infarcts. A second objection to the ischaemic necrosis theory is that in myocytolysis even when coagulation banding is seen in the myocardium, adjacent capillaries are seen to contain blood. Thirdly, true ischaemic necrosis would cause some degree of stromal damage, a feature which is certainly not seen in cytolysis.

From the distribution and histological appearances of these foci of myocytolysis in relation to areas of acute myocardial infarction, it seems more likely that the changes are brought about by a lesser degree of hypoxic injury than is necessary to bring about infarction itself. In other words, although the degree of relative hypoxia present in foci of the myocardium may be sufficient to cause acute degeneration and necrosis, the products of that necrosis do not reach the leucotaxin threshold value required to elicit a polymorph response. The reason for this will usually be that the areas involved are too small, but alternatively it may be that not enough leucotaxin is concentrated in a short enough time.

In an infarct the acute changes are worst at the

centre and progressively less severe as the periphery is approached. This is true too of the myocytolytic focus. Only in the healing stage may we talk of the centripetal nature of an infarct and centrifugal nature of myocytolysis. The reason for this difference is the same as the reason for focal myocytolysis appearing to be a more leisurely and less explosive process than infarction. Myocytolysis is dependent only on autolysis unaided by the heterolysins released from polymorph leucocytes, a factor which determines the marked differences in time relationships. In the infarct, healing occurs from the periphery because in a matter of a few days, it is the peripheral area which is severely subjected to the polymorph exudate followed by intense macrophage activity. In a focus of myocytolysis, the digestion of fibres is dependent only on autolysins and thus the process of healing will follow the distribution pursued by the lytic process (from the centre), and will occur relatively slowly.

Thus in essence, the difference pathologically, between the miliary infarct and focal myocytolysis is the presence and absence of polymorph leucocytes, which may be the clue to the presence or absence of sarcolemmal damage,

the factor on which the question of reversibility and myocardial replacement ultimately depends.

Focal myocytolysis in the hearts of patients of this series has been constantly associated with the factors of relative myocardial hypoxia, be they coronary, haematological or myocardial, or combinations of any of these. The primary diseases have been many and varied. However, it is evident that this degenerative myocardial process is not specific for hypoxic damage. It has been shown to occur in acute diphtheritic myocardial degeneration (fig. 44), in uraemia (Durlacher and Winternitz, 1942), during pregnancy and the puerperium (Gouley et al., 1937), in therapeutic insulin shock (Akert, 1950) and scleroderma (Weiss et al., 1943). Hypoproteinaemia and hypoxidosis were regarded by Keleman (1959) as the important aetiological factors in the production of focal myocytolysis in a girl of two years who at post-mortem was found to have extensive fatty change in the liver, atrophy of the adrenal cortex and generalised hydrops.

Experimentally, focal myocytolysis has been produced in rats in anaemia (Experiment G, pp. 370-375, fig. 73), in hypopotassaemia (Darrow and Miller, 1942; Macpherson, 1956), in cats by oxygen deprivation (Grundman, 1950), in rabbits by the production of hyperthyroidism, tachycardia

or both (Menne et al., 1934), and by Vit. B and protein deficiency in albino rats (Scriba, 1938). In many of these clinical syndromes and experimental situations it is difficult to divorce the relative myocardial hypoxic factors from direct toxic effect.

Thus the conclusion is reached that this lesion represents a morphological result of cellular metabolic failure which may be induced by a direct toxin, or much more often, a deficiency of essential elements of which by far the most common is oxygen.

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"GLYCOGENIC DEGENERATION"

"Vacuolar degeneration" is a term used to describe a myocardial change commonly seen in relation to areas of infarction. Distinct vacuolation is not in fact a feature of the fibres in which this degeneration has taken place. The fibres are usually rather diffusely inflated and poor in fibrils, and these appearances have prompted some authors to use the term "foamy degeneration" (Söderström, 1948). Histochemical demonstration of glycogen in these foamy cells lead to the introduction of yet another term, "glycogenic" degeneration (figs. 49, 50, 135 and 136).

The hearts of the routine autopsy series were examined histologically for evidence of this so-called "glycogenic" degeneration. Following routine staining with haemalum and eosin, sections were examined for the foamy change characteristic of the accumulation of glycogen. Where such a change was seen, two blank sections cut from the block from which the H. and E. stained section was taken, were processed by the per-iodic acid Schiff method of McManus with and without pretreatment with diastase. The P.A.S. reaction was not carried out if glycogen was

not suspected by an inspection of the section stained with haemalum and eosin.

An analysis of the routine autopsy series revealed that in 17.6% of the hearts examined, areas of "glycogenic degeneration" were found. The cases are included in table V, the extent of the glycogenic degeneration being approximately represented in each ventricle by one to three pluses.

In ten of these cases this abnormality was found exclusively in the left ventricle and in only one case was it found only in the myocardium of the right ventricle. The remaining eleven cases showed "glycogenic" degeneration in both ventricles.

Left Ventricular "Glycogenic" Degeneration

Of the twenty-one cases in whom "glycogenic" degeneration was present in the left ventricular myocardium, seventeen of the patients had hearts in which the left ventricular myocardium was hypertrophied. Of the entire series, forty-two examples of left ventricular hypertrophy was found so that in 40.5% of these, glycogenic degeneration was also present.

In the twenty cases (that is, all but one) in whom glycogenic degeneration was present in the left ventricle, there was also evidence of acute healing or healed infarct (as defined on pp. 168-169) in the myocardium of that ventricle. In the one case (N 3600) in whom no infarct was found, the patient died in congestive heart failure associated with severe megaloblastic anaemia (Hb. 4.16 G/100 ml.)

Right Ventricular "Glycogenic" Degeneration

In the one case in whom "glycogenic" degeneration was present only in the right ventricle, the myocardium of this cavity was hypertrophied and acutely infarcted. Of the other eleven cases in whom "glycogenic" degeneration had occurred in the right ventricle, the myocardium was hypertrophied in four, and evidence of acute, healing or healed infarction was seen in six.

In four of the eleven cases neither infarction nor hypertrophy of the right ventricle was present, but all occurred in hearts in which there was evidence of infarction of the left ventricle.

The Relation of Focal Myocytolysis to "Glycogenic" Degeneration.

Of the twenty-two cases in whom "glycogenic" degeneration of the myocardium was found, in sixteen the myocardium also contained foci of myocytolysis.

General Morphological Features

The myocardial fibres in which glycogen accumulation has occurred are swollen to as much as 50 μ in diameter. A central non-staining space gives some of the fibres an appearance of hollow cylinders surrounded by attenuated fibrils, pushed out against the sarcolemma (figs. 49 and 50). The nuclei are compressed and displaced to the periphery of the fibre. In other fibres on cross section there is a moth-eaten appearance as a result of the presence of many non-staining areas by which the myofibrillar complement of the fibre is broken up into irregular bundles, some being pushed laterally up against the sarcolemmal sheath. On staining for glycogen by any of the accepted methods (the per-iodic acid Schiff reaction with and without diastase digestion and Best's caramine stain give reliable results), the

positive staining is seen to be particulate and of greatest density not in the foamy areas of the cell but at the periphery (figs 135 and 136).

It is around areas of infarction that "glycogenic" degeneration is most commonly seen. In fig. 49 a subendocardial zone of "glycogenic" degeneration is seen adjacent to an area of acute myocardial infarction. This zone varies with the age of the infarction, initially being relatively thick and indistinct but becoming thinned and better-defined as the reparative phase proceeds. As healing occurs, this zone tends to break up into foci which persist to be seen in relation to areas of collagen repair.

Although fat may be demonstrable in the myocardium around these areas of "glycogenic" degeneration, it is not present within them.

Discussion

At autopsy, the normal human heart contains little or no stainable glycogen, apart from that of the conducting fibres. However, biopsy specimens of human myocardium such as that of the auricular appendage removed at mitral valvotomy, may contain quite large amounts of glycogen.

Similarly, myocardium from normal, living, fully oxygenated hearts from experimental animals contains stainable glycogen throughout both ventricles and septum, provided the tissue is fixed soon after excision.

The paradox of the last paragraph is related to a speedy glycolysis which occurs following death. After sudden cessation of the rat heart, post-mortem autolysis has been found to result in the disappearance of glycogen in about two hours (Wittels et al., 1959). By contrast, however, these authors found that sustained muscular contraction in the presence of systemic hypoxia caused the glycogen to disappear within about five to fifteen minutes after death. Confirmation of this remarkable phenomenon is available from the many workers who are interested in "early infarction" demonstration. Glycogen depletion has been found to be one of the first demonstrable histological changes to be observed on light microscopy following coronary artery ligation (Yokoyama et al., 1955; Neoral et al., 1959; Kent and Diseker, 1955). In addition cardiac glycogen fractions have been studied biochemically by Merrick and Meyer (1954) following ligation of the anterior descending branch of the left coronary artery of the dog. Four

hours later the heart was removed and a strip of tissue was removed to include normal and infarcted myocardium at each end. This strip was divided into six equal parts varying only in the degree of hypoxia to which each had been subjected. The bound glycogen fractions were then determined chemically and it was found that in the zone of infarction there was a decrease in the total glycogen but the ratio of bound to free glycogen was unchanged from normal. However, the border zone showed a preferential depletion of the free glycogen.

As has been mentioned, normally myocardium obtained at autopsy contains no glycogen apart from that persisting in conducting fibres. This persistence of glycogen within the conducting fibres is of great interest in view of the known high content of glycogen in the Purkinje fibres (Maximow and Bloom, 1952). It was suggested by Yokoyama et al. (1955) that the ability of the Purkinje fibres to survive anoxia may be due in part to the fact that they contain large glycogen reserves and Murray (1954) showed them to have a lower requirement for oxygen than myocardial fibres.

It must be assumed therefore that glycolysis is a speedy process following death. It is brought about by

autolysis, but in view of the remarkable rapidity of the disappearance of glycogen after induced experimental hypoxia it seems certain that an agonal period of cardiospiratory failure will considerably accelerate the process.

Thus the persistence of glycogen in quantity in the human heart must be viewed with some suspicion, a suspicion which heightens to near conviction when the frequency with which this change is associated with relative myocardial ischaemia is assessed.

It could be argued that this form of morphological change represents a stage in a process of slow disintegration of myocardial fibres. However this is unlikely when consideration is given to its distribution. "Glycogenic" degeneration is commonly seen in the zone between the endocardium and acute myocardial infarction. In healed infarction this zone is almost always intact and of normal appearance, so that one can infer that this is an essentially reversible condition. Another notable feature of the histology of glycogenic persistence

after death is that the nuclei of affected cells are usually more prominent than in normal cells. This suggests that although the cell is in a more or less advanced state of degeneration it is not necrotic.

Basically, there are four mechanisms which could bring about an increase in the amount of glycogen seen at post-mortem. First, an abnormally large amount of glycogen could be brought to the myocardial cells; secondly, a mildly injured cell may be unable to metabolise a normal amount of glycogen brought to it; thirdly, glycogen may be abnormally great in amount because of impaired muscular contraction, and lastly the glycogen brought to the cell may be in an abnormal physical state.

That an abnormal amount of glycogen is transported to the heart is unlikely in view of the fact that blood sugar levels in life and at autopsy are normal in some of

the patients in whom abnormally great amounts of glycogen are demonstrable in the myocardium. Similarly in the cases of this series, in no other site was there glycogen accumulation to suggest that the myocardial changes were part of a generalised thesaurosis.

The second possibility is a likelier one. In much the same way as a certain degree of metabolic dysfunction has been suggested to result in fat accumulation within the cell, another, probably lesser degree of metabolic disorder might result in an inability to metabolise glycogen efficiently. If this is the mechanism of the change, it can truly be called a degeneration.

Incomplete or faulty consumption of glycogen because of impaired muscular contraction is really part of the second theory of glycogen accumulation, presupposing a degenerative process within the cell which affects its metabolic ability. It would seem very reasonable to assume that around the zone of infarction the muscle in which glycogen accumulation is so well seen is in fact muscle which contracted much less vigorously than normal myocardium. Cardiac rupture following infarction would be far more common if this were not so.

Fourthly, persistence of glycogen in autopsy

material could be related to an altered physico-chemical state of the glycogen itself. On the basis of different solubility factors in trichloracetic acid Bloom and his colleagues (1951) have suggested that glycogen can exist in more than one form. Similarly Merrick and Meyer have shown chemically that the total glycogen of the myocardium consists of "free" and "bound" fractions about which we know little histochemically speaking, and as Stettin (1959) points out it cannot be assumed that these variants of glycogen will display the same susceptibility to the available autolytic enzymes.

The evidence of this series strongly supports the role of relative myocardial hypoxia in the production of "glycogenic" degeneration. It has been commonly seen in association with manifestly hypoxic lesions of the myocardium. In the few cases in which infarction has not been demonstrated in association with "glycogenic" change it is suggested that coronary, myocardial and haematological factors have combined to contribute to a degree of relative hypoxia sufficient to induce glycogen persistence in the myocardial cells after death. A most interesting example of such a case was reported by Finkelstein (1936) as "Cardiomegalia glycogenica circumscripta". In the heart of this patient the left coronary

artery arose from the pulmonary artery and had resulted in the production of a hypertrophic myocardium in which there were large areas of "glycogenic" degeneration. The same morphological pattern was described in two more examples of this cardiac congenital abnormality reported by Scholte (1930-31) but in these no histochemical demonstration of glycogen was carried out. The hypoxia resulting from the anomalous origin of the left coronary artery was insufficient to cause infarction but enough to cause the cellular abnormality required to result in the post-mortem demonstration of large amounts of intracellular glycogen.

Experimentally, the amount of myocardial glycogen has been varied in many more ways than by reducing the oxygen supply. Although this mechanism may be the underlying factor in severe anaemia, Moses (1944) also produced a similar glycogen depletion in hyperthyroidism, which may well have resulted in a degree of relative myocardial hypoxia similar to that produced by severe anaemia. However, the direct toxic action of the thyroid hormones, or lack of the anterior pituitary hormone, cannot be discounted. Certainly adrenaline (Chang, 1936-37), noradrenaline (Bloom and Russell, 1955), insulin (Evans, 1934;

Cruickshank and Shrivastava, 1930) and cardiac glycosides (Read and Kelsey, 1956) have been found to cause alterations in the amount of myocardial glycogen. Increases in the concentration of glycogen have been reported following fasting (Adrouny and Russell, 1956; Evans, 1934), the administration of growth hormone (Adrouny and Russell; Russell and Bloom, 1956) or pancreatectomy (Cruickshank and Shrivastava).

In a paper on the histochemical observations on glycogen in the human myocardium Wittels and Reiner (1960) concluded that the persistence of glycogen was not dependent on the post-mortem interval, function of fibres, nutritional status, diabetes mellitus, pulmonary disease, heart failure, hyperkalaemia or the administration of cardiac glycosides.

Conclusion

In the use of the term "glycogenic" degeneration it must be emphasised that what is meant is an inability of certain cells to break down their load of glycogen after death. What is sometimes inferred is that these same cells had difficulty metabolising glycogen in life. This may or may not be true. "Glycogenic" degeneration is a

change that is induced by the factors that are responsible for infarction and myocytolysis, operating at a less severe level. It is not, however, a specific lesion of hypoxia. Nevertheless, it would seem from the rarity of the lesion in non-infarcted and non-myocytolytic hearts that it is not easy for normal active myocardium to undergo this change.

"Glycogenic" degeneration occurs readily in myocardium adjacent to areas in which necrosis is taking place and no active contraction is occurring. It is difficult to decide what is cause and what is effect. However, part of the accumulation of glycogen within the cells surrounding an area of infarction may be indicative of inactivity of the cells in an attempt to spare the necrotic zone from undue tearing strains. This strange, localised thesaurosis may well be the morphological evidence of a protective metabolic blockade mechanism which protects the area of infarction from rupture.

The term "glycogenic" degeneration is far from acceptable and until this phenomenon is more precisely understood it would be preferable to describe the change as post-mortem persistence of glycogen.

FATTY CHANGE IN HEART MUSCLE CELLS

Fatty change in the heart may be defined as the demonstration of fat droplets within the myocardial cells on light microscopy. With the use of the electron microscope it has been realised that this definition excludes many cases in which fatty change is present but not sufficiently pronounced to produce a positive fat staining reaction in a frozen section looked at under a light microscope.

The importance of fat embolism in the production of energy in the myocardium has been stressed by Bing (1954) who established that in the fasting state, most of the energy in the heart is derived from this source. As a result of work by Gordon and Cherkes (1956) and Dole (1956) the concept has been developed that free fatty acids are the blood lipid fraction concerned primarily with the supply of fats to tissues for oxidative metabolism, and that the healthy heart can extract fairly large amounts of these acids. It has also been established chemically that a large fraction of total fatty acids removed by the heart is not immediately oxidised to carbon dioxide and water, suggesting the likelihood that fat may be stored in the myocardium (Bing, 1960). A morphological basis to this is

provided by Poche (1959) who described assimilation and degradation forms of fat droplets following a study of the heart of the hibernant, the dormouse. During the feeding up process before the winter, fatty change in the heart is of an assimilation type from which the animal may draw for its source of energy during the seven months during which it lives without food or drink. It is interesting to note that degradation forms of fat droplets appear most commonly towards the end of hibernation and although the general metabolic rate drops to one-seventieth normal, the metabolism of the myocardium only drops to one-tenth. Poche has seen no evidence to support the theory of "phanerosis."

Myocardial cells dying rapidly do not accumulate fat but cells dying slowly may do so. Partially injured cells may be sufficiently intact metabolically to accept lipids from the plasma, but are unable to metabolise them at a rate great enough to prevent the accumulation of neutral fat in the cell. Cells showing fatty change are a feature of the viable border surrounding an infarct and are indicative of the reversible nature of this injury.

A number of papers have been published on the study

of fatty changes that occur in experimental myocardial infarction. Using Sudan III to demonstrate neutral fat in coronary ligation infarcts in dogs, Karsner and Dwyer (1916) did not see fatty change until twenty-four hours after ligation. By the use of oil red O in propylene glycol, Wartmann and others (1956) noted a slight and variable increase of neutral fat in ischaemic myocardium one to three hours after occlusion of a coronary artery; this fat accumulation increased steadily for the next eighteen hours and the fat persisted in apparently viable myocardium for the next fourteen days.

Fatty change is not a specific degenerative change of hypoxia. Bacterial and chemical poisoning may also be responsible. When hypoxic in origin, the distribution of the fatty change is indicative of the distribution of the oxygen debt. The patchy distribution is determined by the distance from the arteries and although in anaemia the "thrush breast" heart is characteristic, the fatty change seen in cases of poisoning and long-standing sepsis is usually too diffuse to produce any macroscopic mottling. There are many reports in the literature describing the development of fatty change in the myocardium during hypoxia without actual infarction. Müller and Rotter (1942) for example found fatty change in the myocardium of German

airmen dying suddenly during high altitude flights.

Fatty degeneration occurring in hypoxic myocardium should not be considered in isolation but in relation to other forms of degeneration and necrosis. From the distribution of this fatty change in and around infarcts or areas of myocytolysis it can be regarded as a metabolic failure in cells subjected to a mild hypoxic injury.

Acute Hypoxic Myocardial Degeneration

As has been discussed the variation of response of myocardial cells to a constant intensity of hypoxia within the centre of an infarct or a centripetally varying intensity of hypoxia as the centre of the infarct is approached, can produce a wide gamut of histological change. Within an area of acute infarction, fibres in which cells are necrotic and from which coagulated protein is undergoing speedy lysis are surrounded by polymorph leucocytes. However, there are also areas in which the fibres show less advanced changes. Coagulation of protein may or may not be demonstrable on haemalum and eosin staining but after the milling yellow and phloxin sequence the differentiation of the degenerate muscle is sufficient to enable the irregular banding and granulation of the coagulated protein to be clearly seen.

It is suggested that these are the changes of acute hypoxic degeneration of the myocardium and are seen in areas in which the discrepancy between the requirement and availability of oxygen to the myocardium is so gross in relation to the time over which it acts that myocardial infarction will occur, or at a lesser intensity of hypoxia,

focal myocytolysis will ensue. It is for this reason that the term acute hypoxic myocardial degeneration is preferable to "early infarction" as a description of this histological pattern. It must be admitted that on histology alone the only description permissable is in fact "acute myocardial degeneration" as an exactly similar change in myocardial cells (excluding stromal appearances) is seen in hearts suffering the effects of the toxin of diphtheria, and in the myocarditides. The epithet "hypoxic" may be added only when the assessment of the myocardial, haematological and coronary factors merits the incrimination of oxygen lack as the aetiological agent.

Foci of "hypoxaemic necrosis" of heart muscle resulting from chronic or acute coronary insufficiency were described by Büchner (1939). The causes include narrowing of the ostia of the coronary arteries, stenosis of the coronary arteries, circulatory shock, severe anaemias, subacute carbon monoxide poisoning, breathing air of reduced oxygen concentration, massive pulmonary embolism and chronic ventricular decompensation. The histological appearances with polymorph leucocytic infiltration of these microscopic foci were in no way different from focal

infarction, and lesions of this type seen in the hearts of this routine autopsy series have been termed microinfarcts, meriting under the "acute infarction" heading of table V, one plus.

The stage at which the term "acute hypoxic degeneration" is applied, occurs before the arrival of the polymorph leucocytes. On the other hand, as has been explained, a neutrophil polymorph response may not be elicited. In such an instance focal myocytolysis results. Whereas Büchner believes that these foci of "hypoxaemic necrosis", or microinfarcts, occur in anginal attacks, it is more likely that "acute hypoxic degeneration" occurs, the extent and "acuteness" of which will determine whether infarction or merely cytolysis will ensue. The importance of this differentiation is considerable, if, as has been suggested (pages 197 and 198) a measure of reversibility may occur in focal cytolytic lesions.

One of the main aims in this study has been to assess the validity of the changes described as "acute hypoxic myocardial degeneration". A study of cases in which these changes have been seen in association with (a) acute

infarction, (b) focal myocytolysis, (c) "glycogenic" and fatty degeneration, suggest that acute degeneration can be considered an authentic if not specific indication of relative myocardial hypoxia.

The histological picture of acute hypoxic myocardial degeneration has already been described on page 176 (figs. 9, 12, 13, 16, 18, 114, 115, 129-134, 141-146). The formation of phloxinophil coagulation bands, between which there are rather granular fragments of coagulated protein can be easily seen in the myocardium stained with milling yellow and phloxin, whereas haemalum and eosin stained sections may or may not reveal a dusky eosinophilia which in small foci is easily missed.

Acute degeneration of the myocardium has been demonstrated in the myocardium of fifty-three patients of the routine autopsy series. It has been seen in the area around every acute infarction in this series, and has been frequently seen in relation to areas of healed infarction (figs. 12 and 142). The myocardium in which focal myocytolysis has been seen also frequently contained foci of acute degeneration which were discrete from the cytolytic lesions.

The left ventricle contained foci of acute degeneration in thirty-nine hearts examined and of these

twenty-four (61.5%) were hypertrophied. Of these twenty-four hypertrophied hearts fourteen (58.4%) also contained evidence of acute left ventricular myocardial infarction. Of all the thirty-nine hearts, twenty-three (59%) contained evidence of acute left ventricular myocardial infarction. The right ventricle contained foci of acute degeneration in thirty-nine hearts and of these fourteen (36%) were hypertrophied, and fifteen (38.4%) showed evidence of acute right ventricular infarction. Of the fourteen hypertrophied right ventricles, six (23.3%) contained foci of acute infarction.

Thus acute degeneration was seen in twenty-four (57%) of the forty-two hearts in which the left ventricle was hypertrophied, and fourteen (43.7%) of the thirty-two hearts in which right ventricular hypertrophy was diagnosed.

A critical examination of not only the associated pathological changes in patients in whom this acute myocardial degenerative change was found in the absence of acute infarction lesions but also their histories has revealed that it is commonly associated with the clinical signs and factors of relative myocardial hypoxia. From the case notes of these patients included in table V,

histories of sudden collapse eight hours before death (N 3411) (fig. 9), acute breathlessness and retrosternal pain for nine hours (N 3436), breathlessness and acute retrosternal pain for thirty hours (N 3445) (fig. 12), acute retrosternal pain for three hours (N 3456) (figs. 132-133), death two hours after an anaesthetic for the pinning of a femur (N 3561) (fig. 130) and a "funny turn" two hours before death (N 3607) (figs. 13 and 14), are typical. Many patients of the series with histories of acute retrosternal pain for twenty-four hours (N 3457) (fig. 131) and chest pain for thirty-six hours (N 3495) (fig. 134) did in fact show not only acute degenerative change but acute myocardial infarction as well. From a comparison of the two groups, with and without infarction, the changes described by the term acute hypoxic myocardial degeneration, are those that would be called "early infarction" by observers who were unaware of the change also being a precursor of focal myocytolysis.

The number of cases in whom acute degeneration has been seen in the myocardium of the right ventricle and tricuspid papillary musculature is high by comparison with the frequency of right myocardial infarction. It may be that the right ventricle is less able to recover

from the effects of these hypoxic lesions than the left, with the result that the patient is less likely to survive to develop recognisable acute infarction. It is certainly very striking that these lesions occur so often in the myocardium of patients with extensive pneumonias (the influenzal haemorrhagic type being particularly dangerous), large pulmonary embolisms (which, as occurred in the case N 3394, fig. 129, do not, however, kill immediately), and in patients with chronic pulmonary disease.

These cases in whom acute myocardial degeneration is seen, may show extensive electrocardiographic evidence of relative myocardial ischaemia. A woman of seventy-five years (N 3393) was admitted with a left hemiplegia which was found at autopsy to be due to a cerebral atherothrombosis. She was not shocked (B.P. 186/96 mm.Hg.) but she was anaemic (Hb. 10.5 G/100 ml.) and had an extensive bronchopneumonia. On electrocardiography a relative ischaemic pattern was reported. At autopsy, the heart and coronary vasculature looked normal, and on microscopy a fine myocardial fibrosis of both ventricles was accompanied by focal acute degenerative change which was more marked in the right than the left ventricle.

As in the case of myocardial infarction, influenza may

be associated with this acute degenerative change. Although it seems likely that the influenzal virus acts directly on the myocardium of many patients with 'flu, the acute changes seen in the hearts of influenzal victims of this series had a distribution which suggests a hypoxic rather than directly toxic action. Only in two cases was an additional diffuse myocarditis noted. One was a woman aged sixty-two (N 3411) who was admitted in congestive cardiac failure having caught 'flu ten days previously. Two days later she began to cough and about a week later noted marked shortness of breath, and became severely ill. She was cyanosed and moribund on admission when she was noted to be in congestive cardiac failure. Influenzal pneumonitis was widespread, but of immense interest were two cardiac abnormalities. First, there were scattered about the myocardium (particularly in the papillary musculature) areas of acute hypoxic degenerative change (fig. 9), and secondly, plasma cells and lymphocytes infiltrated the myocardium. The degenerative change was not morphologically related to the infiltrate and there appeared to be two discrete entities, the myocarditis of influenza and the lesions of acute hypoxic degenerative change brought about by hypotension,

poor pulmonary function, anaemia, and the increased right ventricular load.

A striking example of this degenerative change of the myocardium was seen in the heart of a male of eighty-one years (N 3422) who had what he called "influenza" two weeks before admission. On arrival in hospital he was anaemic (Hb. 6.08 G/100 ml.), anuric, dyspnoeic, and complaining of tightness in his chest. At autopsy he was found to have an organising lobar pneumonia and a bronchopneumonia. He had left ventricular hypertrophy, a bacterial endocarditis and acute myocardial infarction. On microscopy many vessels were seen to contain thrombi, some of which were endothelialised, the appearances suggesting that showers of emboli had found their way into the coronary circulation. The striking microscopical feature was the extent of myocytolytic change and the associated acute hypoxic degeneration, the gradation of the one to the other being illustrated in figs. 36-39. Here was a patient in whom infarction did not follow the acute hypoxic degeration seen leading into an area of myocytolysis in this series of photographs. In other areas, however, acute infarction was seen both in the right and left ventricles.

Acute degenerative change was seen in the myocardium in which lymphosarcomatous infiltration occurred (N 3455) (figs. 47, 60-62). This case is discussed on pages 321 to 323. Although the tumour deposit may have to some extent determined the localisation of this acute degenerative change, fundamentally it was related to the hypoxia (fig. 48) caused by coronary atherothrombosis and broncho-pneumonia. No area of infarction was found.

Extensive acute hypoxic degeneration of the right ventricular and tricuspid papillary muscle was strikingly demonstrated in the case of the fifty-seven-year old male (N 3421), who had suffered from chronic breathlessness since a chest operation for carcinoma of the lung. He was anaemic (Hb. 9.8 G/100 ml.), bronchiectatic and had a terminal broncho-pneumonia in his remaining pulmonary parenchyma. He had normal coronary arteries. Right ventricular hypertrophy was gross and by fibre measurement the constituent fibres were on average thicker in the right ventricle than those on the left. Widespread degenerative change was present in this hypertrophic myocardium (fig. 159) but no such abnormality was seen in the normotrophic left ventricular muscle.

Discussion

The demonstration of acute degeneration of the myocardium demands high standards of histological technique in the fixation, dehydration, cutting and staining of the tissue to be examined. Artefact can result from defects of every stage in the processing of myocardium. Variations in the normal pattern of phloxinophilia can be introduced by inadequate or poor fixation, by straightening a piece of tissue following its twisting during fixation (fig. 8), by inadequate dehydration, by undue hardening (in benzene) and by defects in microtomy. However, the artefacts of the phloxin milling yellow stained section are usually easily recognisable as such and are quite different in distribution and character from the change described as acute degeneration.

From the results of this series in which the histological appearances were strictly concluded in each case before details of the clinical history and macroscopic description of the heart were consulted, acute degenerative change has a high correlation with a clinical history, clinical investigative data and pathological findings of relative myocardial hypoxia. It is wrong to dismiss this change as agonal as it is demonstrably a link in the

chain of morphological changes leading to myocardial infarction and focal myocytolysis.

From the clinical history of one patient (N 3607) this change would appear to have been demonstrable after a death which occurred two hours of the onset of acute hypoxia, described as "a funny turn". In this patient thrombosis had occurred in a grossly atheromatous coronary artery. The thrombus was firm and at one edge endothelialisation was seen. Almost certainly the vessel had been thrombosed for more than two hours, but the clinical onset of impending doom had occurred some hours after the thrombosis. In this series it has been extremely difficult to correlate accurately the time of clinical onset of acute hypoxic symptoms with the pathological changes. There is much variation in the histological patterns in the cases in which apparently accurate clinical histories have been available and it has been impossible to come to a conclusion on this important point. Nevertheless it is fair to say that the recognition of this acute degenerative change will clear the autopsy files of some at least of the cases in whom no message has yet been deciphered on the heart.

Summary

The pathological reaction to hypoxia in the myocardium varies with the degree of injury. A series of recognisable morphological patterns have been described which are considered to result from different stages in the continuum of graded hypoxia which adversely affects the metabolic integrity of the myocardial cells.

Basically these hypoxic injuries result from a disproportion between the amount of oxygen available and the amount required to allow the myocardial cells to fulfil their function. Thus, of critical importance is not the absolute degree of hypoxia but the degree of hypoxia relative to the needs of myocardial function.

The absolute degree of hypoxia is determined by the oxygen saturation of coronary arterial blood, the amount of blood carrying the oxygen and such factors as viscosity which determine the ease with which the blood can circulate. These have been called "haematological factors". The absolute degree of hypoxia will also be determined by the size of the coronary arterial and arteriolar channels, and the adequacy of coronary artery filling from the aorta. These have been called the "coronary factors". Finally the relative degree of hypoxia will be dependent upon how much

myocardium is to be supplied, the efficiency with which it can use this supply and the amount of work that the myocardium must perform. These have been called "myocardial factors".

A summarised scheme of hypoxic injury is given in fig. 125. Myocardial cells may have their metabolism so disturbed that they undergo acute hypoxic degeneration and die, or they may only suffer a disturbance of their metabolism. Cells undergoing acute degeneration imbibe fluid and either the protein content coagulates and lyses, or less commonly lysis follows an acute oedema of the cell in which no evidence of coagulation or protein can be seen. Depending upon the extent of this change (which is fundamentally dependent upon the intensity of the hypoxia relative to the myocardial factors), a polymorph leucocyte response will or will not occur. If it does, heterolysins and autolysins will bring about speedy myocytolysis and stromal damage to allow ingress of the macrophages. This, an infarct, is the morphological pattern which will result in condensation following collapse of reticulin and fibroblastic activity to produce scarring of the heart. If no leucocytic response is elicited, coagulated protein is lysed by autolysins only, and focal myocytolysis will

ensue. The intact stroma may be in part or even wholly recolonised by hypertrophy of adjacent undamaged cells growing along the still intact sarcolemmal tubes. If this fails to occur, collapse and condensation of the area is followed by focal scarring.

A lesser intensity of relative myocardial hypoxia will result in a metabolic upset, resulting in a blockade of carbohydrate or fat metabolism.

Post-mortem glycolysis is speediest in frankly infarcted myocardium. However, around an infarct, post-mortem persistence of glycogen may be the result of diminished activity within these boundary cells or an inability of the cells to metabolise glycogen at the normal rate. Another possibility is that these cells contain glycogen in an altered physico-chemical state. Fatty change will result from an inability of the cell to metabolise fat at the normal rate, resulting in an accumulation of fat within the cell.

These metabolic dysfunction injuries are reversible but may well influence their susceptibility to a

lengthening of the hypoxic phase or an increase in its intensity.

CHAPTER SIX

THE REACTION OF THE MYOCARDIUM TO DIPHTHERIA TOXIN

To study the reaction of the myocardium to a known cardiac toxin, sections were cut from paraffin embedded blocks from the hearts of children who were known to have died from diphtheria.

Although organisms "morphologically identical with Klebs-Löffler bacilli" had been demonstrated in the throats of the thirteen children from whom myocardium was available for study, three cases were excluded from the series, as these young children did not live long enough to undergo Schick testing to eliminate the possibility that they were merely carriers of the disease.

The material studied was collected and kindly given to me by Professor A.C.Lendrum. It dates from the years 1945-47. The tissue blocks, coming from different centres, were primarily fixed in a variety of ways. All were secondarily fixed in saturated corrosive.

Brief clinical details of the series together with immunological and bacteriological information where available, are given in table XII. Abstracts from the original clinical notes are given in Appendix B (Volume II) together

with the cardiac macroscopic and microscopic descriptions.

Results

It is unfortunate that full macroscopic descriptions and weights of the hearts of this series are not available. The only macroscopic changes noted were subendocardial and epicardial petechial haemorrhages, some myocardial haemorrhage and in some cases, mural thrombi in the ventricles.

Microscopically, the extent of the myocardial changes in general varied with the length of the illness. In cases dying in the first week to ten days, the outstanding change was an interstitial oedema, the perivascular distribution of which was frequently infiltrated by plasma cells, lymphocytes and occasionally a few neutrophil polymorphs. This confined cellular infiltrate was not seen among the muscle bundles, although rather bubbly areas of oedematous change could be made out in these areas. The cells of the interstitium and of the capillary endothelium were prominent and plump.

By the twelfth day, in addition to the interstitial changes and rather overshadowing them, extensive and

and strangely cellular, hyaline degenerative changes were seen within the muscle fibres themselves (fig. 20). Individual cells appear to undergo degenerative change in which adjacent cells may or may not share so that the characteristic appearance of this toxic change in the heart is cellular degeneration occurring apparently haphazardly along the length of the muscle fibres (fig. 23, 31). In more severely affected areas, longer segments of muscle fibres are affected (figs. 21, 22, 26,27 and 30).

The progression of the degenerative process in the muscle produces in places a loose stromal net infiltrated by macrophages and small round cells (figs. 25 and 29). Myolysis is now a prominent feature (figs. 26 and 27). The heart has a peculiarly moth-eaten appearance and in some areas there is little more than the pre-existent stroma surrounded by an infiltrate of histiocytes, plasma cells and lymphocytes. At this stage, areas of hyaline degeneration are less commonly seen than in the earlier phases.

By the middle of the third week the fibrosis of this essentially reparative inflammatory process is seen. Fine fibrosis occurs in relation to the damaged fibres.

The heart of one patient (S. 8.) in whom sudden cardiovascular collapse had occurred about eighteen hours before death, contained an early microinfarct in a tricuspid papillary muscle of the right ventricle. The distribution of the pattern of shredded coagulation together with adjacent vascular margination of leucocytes was quite unlike that of an uncomplicated diphtheritic lesion. No coronary disease was present.

Exception to the timing of these changes was provided by the heart of the three-year old boy (S. 5.) who was said to have a history of the disease lasting four days. The advanced myofibrillar degenerative pattern was more like that of the children who had had diphtheria for fourteen to sixteen days. Another exception was the three-year old boy (S. 6.) in whose heart the only abnormality found was an area of endocardial mural thrombosis and a few subendocardial haemorrhages. This child had had scarletina which was followed by diphtheria, on the seventeenth day of which he died.

Comment

Although clinical detail is lacking in this series

of cases of diphtheria a few points are worth comment. The average length of the illness in fatal diphtheria in a large series of cases is between six and twenty-four days. In Gore's (1948) report of two hundred and twenty-one cases, 75% of the cases came within these limits. In the present small series, the average is 12.7 days from the onset to death, six of the cases having a time interval of nine to seventeen days, three between two and four days and one with an onset to death time of thirty-five days.

In none of the ten cases was the heart found to be microscopically normal, although in general, with the exception of two cases, the degree of myocardial injury rose progressively with the length of the fatal illness.

Signs and symptoms of seriously impaired cardiac function were present in all the cases in which extensive myocardial abnormalities were found at autopsy. The one case in whom there was the "deceptive interval of apparent improvement" noted by numerous authors, was a twelve-year old boy (S. 14), who went into congestive failure after doing well for the ten days after antitoxin treatment was started. After four days in

failure he died.

The earliest changes in the degeneration process have not been, and cannot be, studied in paraffin embedded material. Almost certainly the first changes involve the mitochondria and occur very early in the course of the disease. However, fatty degeneration is a frequent and early change (Councilman et al., 1900; Warthin, 1924) and in an occasional instance of death early in the illness, according to Gore (1948), fat stains delineate foci of degeneration which are not apparent in routinely stained sections. It is particularly unfortunate that fat staining was not possible in the present series if only to estimate the relative merits of fat and myofibril staining in the demonstration of early myocardial changes in this toxic process. The outstanding myocardial degenerative change is a coagulation process which results in the formation of a diffuse hyaline mass within the myocardial cells. This is a change which is strikingly demonstrated by the phloxin milling yellow staining method (figs. 20-24). The coagulated proteinous material breaks down to form irregular and rather indiscriminately arranged "coagulation bands" between which granular material can be seen giving the degenerate fibre a bamboo-stem appearance (figs. 21 and

22). Lysis occurs over the next fortnight to three weeks and is apparently almost entirely an autolytic process rather than one to which heterolysins from neutrophil polymorphs make any significant contribution. The remarkably restricted focal nature of the process is striking, many fibres being apparently involved cellularly at various points along their length without the gross involvement of the sarcolemmal sheath, (fig. 32).

The stromal inflammatory reaction was seen mainly in zones adjacent to muscle in which most cells had been involved in the necrotic process. The inflammatory cells were mostly mononuclear, although a few neutrophils, mast cells and eosinophils were present (figs. 25, 28 and 30). Of interest were the histiocytes of the Anitschkow myocyte group. These cells not infrequently have a remarkable similarity in their nuclear pattern to cells of the myocardium (fig. 33), and their relation to dead and dying cells certainly raises the question of their role in myogenesis.

Discussion

It was Löffler in 1884 who first enunciated the

theory that the heart was attacked by the toxin of the diphtheria bacillus which remained confined to the area of the throat. A few years later, Roux and Yersin (1888) isolated this toxin which, when injected into experimental animals, caused heart failure in the absence of the organisms from which it was derived. How this heart failure was brought about was a subject discussed and argued about for the next fifty years.

Following experiments on rabbits injected with diphtheria toxin Romberg and his colleagues (1899) found that by compressing the aorta and the splanchnic veins, these animals could be revived. They considered that a cardiac death from diphtheria resulted from a fall in blood pressure mediated by direct toxic action on the vasomotor centre in the brain. On the other hand, Brodie (1899) and Friedemann (1932) considered that the frequently fatal hypotension resulted from the diphtheria toxin acting directly on blood vessels and the peripheral vasomotor nerves. By artificially increasing the blood pressure in the aorta and perfusing isolated hearts from diphtheria poisoned dogs, McCallum (1914) was able to keep these hearts beating or to resume beating for hours after circulatory collapse or even death. Thus there

seems no doubt that vasomotor paralysis whether central or peripheral, can cause death by circulatory failure without demonstrable myocardial damage.

The second possible mode of action of diphtheria toxin in the production of cardiac failure is by its effect on the peripheral nerves to the heart. Degeneration of the vagus, the cardiac ganglia and sympathetic nerves to the heart were described by Veronese (1893) in cases of diphtheria dying in cardiac failure. These findings were supported by Vincent (1894). Although diphtheritic myocardial degeneration was noted by Thomas and Hibbard (1900), these authors considered that the nervous lesions were observed earlier and with greater constancy than those in the myocardium which they suggested were secondary to vagal injury. However, many of the early investigators (Leyden, 1882; Unruh, 1883; Huguenin, 1888, Hochhaus, 1891) were unable to demonstrate changes either in the vagi or the ganglia. In an attempt to dispose of the theory that myocardial damage is secondary to primary nerve damage once and for all, Gore (1948) noted that in his own series of cases the numerical and chronological differences between

diphtheritic myocarditis and neuritis were incompatible with any hypothesis which ascribes morphological cardiac changes to nerve injury. Furthermore, other conditions which at times affect the nerves supplying the heart do not cause the myocardial changes observed in diphtheria. Among such conditions are poliomyelitis, the Guillain-Barre syndrome, and a variety of tumours arising from or metastasising to the region extending from the base of the skull to the upper mediastinum. It seems reasonable to conclude that the myocarditis and nerve degeneration seen in diphtheria are not causally related to one another.

That damage to the myocardium itself was of importance in the production of cardiac failure in diphtheria was very much doubted by McCallum (1914) and Donnerstag (1932) who stated that the gross and microscopic changes in the heart were insignificant. Cloudy swelling and some focal fatty change were the only common lesions noted in hearts of diphtheritics by Loth (1923) who stated that a true myocarditis was only exceptionally demonstrable. However, severe and extensive changes have been described by many authors (Councilman et al., 1900; Price and Mackenzie, 1912; Aviragnet et al.,

1918; Warthin, 1924) and many authors have considered that these changes were sufficient in themselves to account for gross cardiac insufficiency.

There is no doubt that the myocardial damage caused by diphtheria toxin can be extensive, and must be inflicted by a direct assault on the metabolism of the myocardial cell rather than mediated through nerve degeneration. Our methods of examination are crude and although patients may die in the first day or so in peripheral failure, the myocardium may already be in a site of considerable metabolic derangement, the morphological result of which is only detectable by light microscopy from about the fifth or sixth day. Evidence for early myocardial involvement comes mainly from electrocardiographic and biochemical demonstration of myocardial abnormality. A recent paper on this subject is that of Charlier et al. (1959) who reported two cases of diphtheritic myocarditis with recovery, and one fatal case. Full electrocardiographic illustrations are given and the depression of the ST segment seen with the onset of clinical evidence of cardiac decompensation confirms the reports

of Andersen (1934), Burkhardt (1938) and Gore. An early rise in transaminase levels have been shown by Chesler (1958) to occur in diphtheria.

Thus in a few cases a fulminating type of infection can overwhelm the patient in a matter of two or three days. Death is due to a peripheral type of vascular failure with little evidence of abnormality in the heart. However, much more frequently, although demonstrable morphological changes tend to lag behind the rapid fall-off in function, electrocardiographic and biochemical evidence of extensive early toxic damage to the myocardial cells is demonstrable.

The phloxin milling yellow staining sequence demonstrates the considerable extent of myocardial damage which is by no means so apparent in sections stained in the routine way.

No accurate anatomical localisation of the distribution of this toxic myocardial degeneration process was possible in the cases of this series. In general, however, the inner portions of the myocardium and papillary musculature were most extensively involved. Although

in one case heart block was noted clinically, there was no evidence to suggest that the conduction system was more or less susceptible than other parts of the myocardium. Numerous authors have described the involvement of the conduction system and Farr (1920) went as far as saying that diphtheria toxin has a specific affinity for the bundle of His. However, as usual on the subject of heart changes in diphtheria, it is not difficult to find another authority who will state exactly the opposite view. Rohmer (1912) expressed his conviction that the diphtheria toxin showed no affinity for the bundle. Perhaps the most interesting observations on this point are by Aviragnet and his colleagues (1918) who were not regularly able to find bundle lesions in cases in which there had been clinically demonstrable arrhythmias.

The next great controversy in this subject raged over the relative importance and frequency of the parenchymatous and interstitial lesions of the myocardium. Although the majority of authors regard a toxic parenchymatous myocarditis as the primary and important lesion

and the changes in the interstitial tissue as secondary and of a reparative nature, Leyden, who found diffuse and overwhelming round cell infiltration in the interstitial tissue of the myocardium and only slight fatty change in the muscle fibres, attributed the cardiac failure to an interstitial myocarditis; Birch-Hirschfeld (1878-79) considered that the interstitial changes were primary and the parenchymatous changes were secondary. Rabot and Philippe (1891) stated that in their series, diphtheritic myocarditis was of the interstitial type. Of interest in relation to parenchymatous damage is the fact that relative myocardial ischaemic lesions cannot be rare in a heart in which there is widespread degeneration, oedema and cellular infiltration. A multiplicity of factors can be invoked to act with the obviously mechanical difficulties of supplying oxygen to the depths of a grossly abnormal mass of muscle. The already damaged heart is not only beating at an abnormal rate but also the peripheral vasodilatation of fever and a diseased myocardium will considerably alter the haemodynamics for optimal coronary artery filling. Of considerable importance too is the fact that a very high proportion of the children are hypoxic due to the local diphtheritic

infection of the throat and/or a secondary pulmonary infection.

In summary, from the evidence of this series, diphtheria causes a myocardial cellular degeneration which is responsible for an interstitial inflammatory reaction which is seen before light microscopy can demonstrate the abnormality in the myocardial cells. After the appearance of interstitial changes, the continued process of myocardial degeneration becomes histologically demonstrable.

The modern opinion among cardiologists seems to be that should a person recover from the acute infection of diphtheria even though cardiac involvement occurs, permanent detectable abnormality of circulatory mechanisms is very unlikely. Cases in which permanent heart block has developed after the onset of diphtheria (Jones and White, 1927) are uncommon enough to merit a case report in the literature. Calcification of the myocardium is another rare complication of diphtheria (Ceelen, 1919; Kratzeisin, 1920) but experience of this disease has been in general agreement with Jones and White's assessment of the myocardium of one hundred young people

who had had severe (70%) and moderately severe (30%) diphtheria, five to eight years before examination. In no case was there evidence of an appreciable chronic effect of diphtheria.

This clinical experience may be related to the essential nature of the pathology of the myocardial injury inflicted by the toxin of diphtheria. The first point to be considered is that there is a remarkable range of sensitivity of myocardial cells to a given level of toxin. No areas of massive necrosis are seen. Cells are picked out by the toxin individually or in relatively small groups. Although as has been stated, certain areas of the heart are more extensively affected than are others, in general the apparently haphazard cellular involvement is seen throughout the myocardium of both ventricles and auricles. Stromal damage is minimal (fig. 32) and in the inflammatory infiltrate there is seldom more than a few neutrophil polymorphs. The products of degeneration within the cell are disposed of by an essentially autolytic process cleansing the area in preparation for repair.

If the myocardium is to be returned to normality some degree of muscle regeneration must occur. Statements

by Anitschkow (1915) and Heller (1914) to the effect that true muscle regeneration occurs were based on Anitschkow's belief in the myogenic function of the "myocyte". Evidence of muscle regeneration was seen in three of Warthin's cases of two, three and three weeks duration respectively. He stated that "Near the necrotic or degenerated portions of the heart muscle, the nuclei of the muscle show a great variety of size and form." Warthin confirmed that all the appearances illustrated by Heller were seen. "The defects in the muscle caused by hyaline necrosis may ultimately have been bridged by a number of new muscle bands apparently uniting with the living muscle on the other side of the defect. The sharp delimitation of the muscle in perimysial or sarcolemmal tubes was shown in our cases as in those of Anitschkow and Heller." Warthin was particularly impressed by a close similarity between the process of regeneration of the heart muscle and that of peripheral nerve trunks. This is a most interesting observation and the basis of an attractive and feasible theory of muscle degeneration. If one imagines necrosis of two cells in adjacent fibres as shown in fig. 34, followed by

their autolysis, by which the entire content of the cell and the protomembrane are lysed and absorbed, the perimembrane remains. Adjacent cells by the addition of sarcomeres and a corresponding increase in girth (true hypertrophy), could grow along the perimembranous canal, to replace the lost cells. In the same way, four myocardial cells in relation to an anastomosis site shown diagramatically in fig. 35 to be necrosed, could be replaced in the same way by adjacent cellular growth. This mechanism would only be possible in the absence of stromal necrosis or reticulin collapse. Thus if this theory is correct, there must be some critical extent of damage beyond which stromal collapse cannot be prevented and focal myocytolysis (fig. 46) with stromal collapse, reticulin condensation and focal scarring will ensue. Secondly, it is possible that if the toxic necrotic myocardial process reaches a stage severe enough to cause stromal damage or to elicit a leucotaxic effect on neutrophil polymorphs, the heterolysins released could well inflict heavy damage on stromal tissues, not only destroying the preformed scaffolding for muscle replacement, but also producing a degree of fibrosis in excess of that

resulting from focal post-cytolytic scarring following reticulin collapse. It is difficult to believe that the fine interfascicular fibrosis laid down in the reparative phase of diphtheritic myocardial involvement is a significant permanent embarrassment to the heart. At best it is of apparent unimportance in the restoration of the heart to functional normality.

This theory of myocardial cell replacement by adjacent cell growth has been hinted at by Warthin (1924) among others, but it is a theory difficult to prove. The degree of hypertrophy required to replace individually autolysed cells would not be great when shared out among the constituent cells of a fibre and one imagines that a shuffling movement of cells to each of which a few sarcomeres had been added would result in such a small increase in thickness of the fibre that it would be well nigh impossible to assess this by present-day micromeasuring techniques. Histologically, and of course clinically, it is an attractive theory which fits the facts. However, it must not be considered as a specific mechanism in diphtheritic hearts. It may well occur following other degenerative necrotic lesions of the myocardium.

"Abortive regeneration", adjacent to areas of scarring, myofibrillar hypertrophy and nuclear enlargement, distortion and hyperchromatism, was noted by Gore. In the present series I have seen no mitoses in the cells of the myocardium but nuclear variation of size and shape was gross and if recolonisation of empty sarcolemmal sheaths occurs by adjacent cell hypertrophy, the stimulus for this growth must be provided for by the emptiness of adjacent zones of the sarcolemmal sheath or the dilatation associated with scattered muscle cell necrosis of diphtheritic affection of the heart. Longitudinal splitting of muscle fibres is a mechanism suggested by Heller by which lost muscle can be replaced. The longitudinal splitting of muscle bands was mentioned by Warthin (1924) as an important step before "these bands grow into the perimysial tubes filling these up, replacing cell detritus and communicating with the living muscle on the other side of the defect."

Evidence of mitotic activity in the myocardium following the death of cells is hard to find. Nevertheless

MacMahon (1937) described the heart of a child who died of diphtheria, in which mitotic figures were found in abundance in the cardiac muscle nuclei. Myocardial regeneration was studied by Ring (1950) in experimental ischaemic lesions in the rabbit, and the cat. Occasional mitotic figures were seen, but he states that regeneration was aborted by the absence of a sarcolemmal framework along which the new fibres might grow.

Conclusion

From a study of material from ten cases of diphtheria and a survey of the literature, it appears that toxic damage to the myocardium results in a parenchymatous degeneration in myocardial cells followed by interstitial cellular reaction. The degenerative changes are well demonstrated by the phloxin milling yellow staining method and are accompanied usually by little stromal damage. It is mainly for this reason that replacement of myocardium results from adjacent cell hypertrophy, regeneration of myocardial cells by longitudinal splitting or by mitotic regeneration. The evidence of this series supports the concepts of adjacent cell hypertrophy and

longitudinal splitting, no evidence of mitotic activity being seen. The importance of these reparative changes is that in most cases the heart affected by diphtheria returns to functional normality.

CHAPTER SEVEN

MYOCARDITIS

In the routine autopsy series under review, in fifteen cases evidence of inflammation of the myocardium was seen. These examples of myocarditis are discussed under four main headings.

1. Rheumatic myocarditis, of which there was one case showing evidence of rheumatic activity and three in which the evidence of past rheumatism was seen.

2. Organismal myocarditis, (a) where no specific organism was demonstrated or incriminated, of which there were three examples.

(b) where specific organisms, protozoa, fungi, bacteria, viruses or helminths were demonstrated or incriminated by bacteriological, immunological, histological or clinical methods. Three such cases are discussed.

3. Chemical or toxic myocarditis, four examples of which were seen.

4. "Isolated" myocarditis, of which no examples were seen.

Rheumatic Myocarditis

Four cases of rheumatic disease of the heart were found in this routine autopsy series. All had abnormal heart valves and in one case Aschoff bodies were seen on microscopy of the myocardium. It was in the heart of this patient (N 3773), a woman aged thirty-three, that the tricuspid, mitral and aortic valves were grossly stenosed. In one case (N 3581) only the mitral valve was affected but in the other two (N 3392 and N 3387), the aortic and mitral valves were involved.

None of these cases was complicated by bacterial infection of the valves.

Two other examples of aortic stenosis were found in the routine autopsy series (N 3689 and N 3470) but both were considered to be atheromatous in aetiology, in view of their calcified nature, the gross atheromatous change in the adjacent aorta and an absence of a history and other stigmata of rheumatic disease.

In only one of the four rheumatic hearts of this series was there evidence of activity in the myocardium. In the heart of the youngest patient in the rheumatic

group (N 3773), not only were Aschoff bodies at various stages of development found but also there was a diffuse interstitial myocarditis, the cellular infiltrate of which consisted mainly of lymphocytes, a few plasma cells and Anitschkow myocytes. In the other three cases perivascular, reticular and occasional focal areas of fibrosis were seen in the myocardium in which a scanty lymphocytic infiltrate in and around the fibrous tissue was found.

Non-specific myocarditis

The popularity of "myocarditis" as a diagnosis and cause of death waned rapidly after the acceptance of the role of diseased coronary arteries in the production of myocardial necrosis, inflammatory cell infiltration and fibrosis. The ease with which macroscopic evidence of necrosis and fibrosis could be correlated with coronary atheroma soon led pathologists and clinicians to believe that true myocarditis in fact was a rarity except in association with rheumatic fever and diphtheria, and no less an authority than Sir Thomas Lewis (1943) stated that the use of the term "myocarditis" was scarcely just-

ified clinically except, of course, in respect of rheumatism.

"Myocarditis" became what Edens (1929) in a monograph on the heart, called "The Stepchild of Pathology" and Saphir titled one of his papers "Myocarditis, a Neglected Subject" (1948).

It is largely as a result of the painstaking and meticulous work of Otto Saphir over some twenty-five years that more and more clinicians and pathologists are being made aware that myocarditis "is a common complication of various infectious diseases and that not too rarely, is the main clinical entity governing all clinical symptoms and thus, per se, responsible for the death of the patient" (Saphir, 1958). He stated in 1948 that true myocarditis is encountered in routine autopsy examinations in about fifteen per cent of all patients autopsied in a general hospital, but ten years later the figure he quoted in his textbook had dropped to between four and nine per cent. No other workers interested in this problem have managed to match Saphir's incidence figure of 1948, but in a careful study by de la Chapelle and Kossmann (1954), myocarditis was found in about ten per cent of the autopsies in

a general hospital.

Much of the variation in incidence of this disease can be accounted for by the varying enthusiasm of pathologists to make the diagnosis. The morphological criteria of "myocarditis" are by no means agreed. In an editorial to the American Heart Journal (1959), Saphir quotes H.A.Christin who summarised the confusion perfectly when he stated, "If by acute myocarditis is meant an actual inflammatory process of the myocardium with infiltration by polymorph leucocytes, this is a rare condition and consequently of minor clinical importance. On the other hand, if by acute myocarditis is meant the circulatory disturbances with or without evidence of degeneration of the muscle fibres or cellular infiltration between them, associated with acute infectious diseases, it is a frequent occurrence."

The term "myocarditis" must be limited to describe myocardium in which there are the classical constituents of acute, subacute or chronic inflammatory exudates. There has been much needless discussion about the differentiation of parenchymatous from interstitial myocardial inflammation. Karsner (1955) does not consider that

any distinction is justifiable and from a later part of this discussion it will be seen that it is doubtful if the distinction is possible.

Having accepted the necessity of an inflammatory exudate for the diagnosis of myocarditis, the next question to be asked is what constitutes an inflammatory exudate? Serous oedema in the myocardium is traditionally difficult to assess histologically, and as the protein content of the exudate may be slight, diagnosis must be based on the cellular content of the infiltrate. A polymorphnuclear cellular reaction establishes the acute, if less common, type of myocarditis but to diagnose chronic myocardial non-specific inflammation, great caution must be exercised. A few perivascular lymphocytes, or a focus of these cells, is slender evidence on which to base the diagnosis of a chronic inflammatory reaction in the myocardium. The significance of lymphocytes whether in portal tracts in the liver, in the endometrium, in certain tumours, in the adventitia of the coronary arteries or in the myocardium is by no means certain, and I have little doubt that this is the root of the problem of the variation of incidence of this disease.

In the diagnosis of chronic inflammation the plasma cell has much more significance than the lymphocyte. The anatomical site in which this problem is encountered most frequently in routine histological work is probably the endometrium where chronic non-specific inflammation diagnosed only when lymphocytes are accompanied by plasma cells, has a high correlation with the clinical course of the patient, whereas this diagnosis based on the recognition of lymphocytes only, is meaningless. By searching through many sections of myocardium, focal and sometimes scanty diffuse infiltration by lymphocytes is a not uncommon finding. A good example of this is illustrated in figs. 151 and 152, showing two foci of lymphocytes which were found in thirty blocks of the heart of case N 3420. Although the significance of these is not known, it is far from proved that their presence had any effect on the action of the myocardium.

Macrophages are of immense importance in the diagnosis of a myocarditis. Whether of the classical "cardiac histiocyte" morphology of Anitschkow or the less easily recognised large mononuclear type, their presence in the myocardium is of the highest significance.

There is no doubt that by the examination of a large number of blocks of each heart, the incidence of this disease is found to be by no means insignificant. By the

examination of one or two histological sections of the heart, it is not unreasonable to suggest that a disease such as myocarditis will be seldom diagnosed. By a thorough search in four or five sections cut from each of twenty-five to thirty blocks, the chances of seeing foci of inflammatory change are increased, but even then it must be appreciated that by this massive task, only a small part of the myocardium is being examined. As Saphir has repeatedly pointed out, the finding of one or two foci of inflammation must be multiplied by the ratio of the mass of the heart not yet examined to that of the sections looked at to obtain some idea of the extent to which the myocardium is involved.

Another practical difficulty in the diagnosis of myocarditis is confusion with the histological pattern of myocardial infarction. Diffuse acute myocarditis with a prominent leucocytic reaction is distinguishable from the centre of an acute infarction by the lesser degree of muscle necrosis. However, neutrophil polymorphs are by no means strictly confined to the area of infarction. The surrounding zone of viable muscle may become quite markedly infiltrated and on section through such a zone the appearances may be indistinguishable from a focus of

acute myocarditis. This problem is mainly seen in relation to small areas of acute infarction, and is only solved by cutting deeper into the block and inspecting sections cut from adjacent and distant areas.

The diagnosis of non-specific myocarditis is beset by many problems and in the routine series of autopsies three cases have been seen. The first two patients were chronic bronchitics in whom non-specific myocarditis was associated with an extensive broncho-pneumonia.

In a study of sixty-seven hearts of patients dying of pneumonia, Saphir and Amromin (1948) found that in twenty-six of these (38.8%), there was a myocarditis. Of the twenty-six cases, twenty-two had "non-specific broncho-pneumonia", seven of these being confluent in type. The variety of organisms cultured from the lungs included non-haemolytic streptococci, staphylococcus aureus, staphylococcus albus and haemolytic streptococci.

For years one of the therapeutic problems of pneumonia has been whether or not to give digitalis to these patients, and it is surprising to find that so little work has been done in the study of the changes seen in the myocardium in

pneumonia.

Of the present series the first case was an eighty-three-year old retired carter (N 3419) who had had bronchitis for years. The only clinically detected cardiovascular abnormality was a rapid atrial fibrillation with the E.C.G. changes of ischaemia "due to rate". At post-mortem, acute bronchitis, bronchiolitis and broncho-pneumonia were found with evidence of chronic bronchitis. A penicillin resistant staphylococcus was grown from the exudate found in the bronchi. The myocardium macroscopically showed no abnormality but microscopically perivascular plasma cells and lymphocytes were seen together with a scantier diffuse intiltration by these cells and macrophages, some of which were of the Anitschkow myocyte group. There were a few polymorphnuclear leucocytes in the exudate and the left ventricular myocardium was mildly fibrosed.

The other case was a fifty-seven-year old male (N 3444) who died the day after his admission in cardiac failure. He had been a chronic bronchitic for years, and had an emphysematous chest and right ventricular

hypertrophy. In addition to a lymphocytic and plasma cell infiltration of the myocardium of the heart, areas of acute hypoxic degeneration were seen in the myocardium of the right ventricle and tricuspid papillary musculature. A dense lymphocytic infiltration of the epicardium was also noted. These two alone, of many cases of broncho-pneumonia seen in the series showed myocardial inflammatory change, and only one of them was in failure.

It may be fairly asked if there is any real significance in the recognition of chronic inflammatory cell infiltration in the myocardium. It was Saphir and Amromin (1948) who pointed out the extensive literature which exists on the evaluation of cardiac stimulants in cases of pneumonia. It certainly seems that the older physicians were impressed by the problem of cardiac failure in pulmonary infections, but it is doubtful if this is due to myocardial inflammation. The evidence of this series points to right ventricular hypertrophy and relative hypoxia of the right ventricular myocardium as the main causes of congestive failure in association with lung disease in these patients many of whom are already

pulmonary cripples.

The third patient in whom non-specific myocarditis was diagnosed was a woman (N 3403), aged seventy-three years, who was admitted with severe abdominal pain and died thirty-six hours later. It was suspected that her pain was myocardial in origin and an electrocardiogram was reported as "A rather unusual pattern suggestive of posterior myocardial infarction." At post-mortem in the heart, severe coronary atheroma, both right and left myocardial hypertrophy, and a healed left ventricular infarction were found. On microscopy acute infarction of the left ventricular papillary musculature and acute hypoxic change in the left ventricular myocardium were found in association with a patchy myocarditis. The inflammatory changes were focal and the macrophage and occasional giant cell cellular reaction was striking (figs. 149-150). These lesions were not specifically confined to the areas of infarction but were few in number and seen in only three of the twenty-eight blocks of tissue cut. A generalised peritonitis from a perforated chronic duodenal ulcer and fat necrosis of the pancreas accounted

for the abdominal symptomatology and the appearances suggested to Dr. Attwood, who carried out the post-mortem examination, that leakage from the ulcer into the peritoneal cavity had preceded frank perforation. There is no detailed history of the patient's health in the week before the onset of severe abdominal pain although she is known to have been a dyspeptic for some five years.

No explanation for this focal granulomatous myocarditis can be offered other than that it was in some way related either to the peritonitis which had been present for much longer than thirty-six hours if only in a localised form, or perhaps to the pancreatic necrosis.

Specific Organismal Myocarditis

Myocarditis may result from the invasion of the myocardial tissue by protozoa, fungi, bacteria or viruses. In the routine autopsy series under review, three examples of myocarditis due to a specific organism were seen.

Bacterial Myocarditis

The one example of a myocarditis resulting from pyaemia was provided by a woman, aged thirty years (N 3501) who was admitted for portocaval anastomosis, to relieve portal hypertension caused by a cirrhosis of the liver. Following the operation she went into liver failure and died. At autopsy small pyaemic abscesses were found in the myocardium and kidney, the infecting organism being a staphylococcus of the so-called "hospital" type. In addition to the pyaemic abscesses, there were areas in which the myocardium was diffusely infiltrated by polymorph leucocytes.

As elsewhere in the body, abscess of the heart may result from dissemination from a distant focus or by direct extension of an infectious process in the organ itself. In the myocardium, abscess is more frequently seen as part of an overwhelming pyaemia. In general hospital practice today, most examples of this disease are seen in post-operative patients and recently a rise in the incidence of post-operative fungal infections has been noted in this hospital. Very recently two examples of post-operative generalised moniliasis have been

seen. Both patients died following resection of carcinoma of the oesophagus. In neither case was there any evidence of more than a minimal reaction to the fungus in the heart. However, no example of fungal or protozoal myocarditis has been found in this routine autopsy series.

The second mode of infection occurs from bacterial endocarditis in the acute form of which Sheldon and Golden (1951) showed that the myocardium was commonly involved. Three examples of bacterial endocarditis were seen in the routine autopsy series, but in none of them was abscess formation seen.

The first of this group was a male patient aged thirty-six (N 3405) who had had poliomyelitis in 1951 when his legs and intercostal muscles had been paralysed. He spent three months in a respirator and made a moderately good recovery. In the course of a severe respiratory infection in 1959 he developed a degree of respiratory difficulty which necessitated his emergency admission to hospital. A tracheostomy was performed, and he died two weeks later. At autopsy a necrotising and in places organising pneumonia was found, affecting

all the lobes of both lungs. A terminal bacterial endocarditis involved the mitral and aortic valves.

The myocardium was extensively focally infarcted. Although the coronary arteries showed no evidence of atheroma, microscopically many of the smaller coronary radicles were seen to contain fibrinous thrombi, some of which were contracted and endothelialised causing only partial luminal occlusion. Most of the lesions were of embolic origin, and no areas of abscess formation were seen. Focal areas of acute hypoxic degeneration were widespread as were zones of focal myocytolysis and glycogenic vacuolation of both the myocardium of both the right and left ventricles.

A terminal bacterial endocarditis was also seen in a male patient, aged eighty-one (N 3422) who was admitted in urinary retention but was found at autopsy to have an organising lobar pneumonia. Friable vegetations containing bacteria of morphological identity with the pneumococcus were found in apparently previously normal mitral and aortic valves. The left ventricular myocardium contained foci of acute hypoxic degenerative changes as well as those of glycogenic vacuolation and extensive

myocytolysis. Emboli were seen in many of the intramyocardial coronary radicles.

The third of the examples of this disease occurred in a fifty-nine-year old male (N 3429) who had a fourteen year history of rheumatoid arthritis, and died of an extensive necrotising broncho-pneumonia and widespread infarction of the heart. The coronary vasculature was severely atheromatous and a recent anterior descending coronary thrombotic occlusion was found. The mitral valve was the site of small verrucous vegetations which, however, were friable and described at autopsy as "bacterial". The acute myocardial infarction of the anterior wall of the left ventricle extended into the septum and microscopically the right ventricular myocardium was found to be involved as well. Acute hypoxic degenerative change (figs. 145 and 146) was found as well as foci of myocytolysis and glycogenic degeneration. Only one intracardiac vessel containing thrombus was seen.

Probably these three cases (certainly the first two) were terminal. From the histology of the myocardium there seemed no need to invoke a "myocarditis" to account for the changes seen. In the third case embolism may have contributed to the thrombosis of the grossly athero-

matous coronary arteries to produce extensive infarction.

Virus Myocarditis

In 1945 Helwig and Schmidt (cited by Schmidt, 1948) isolated a virus from a group of anthropoid apes dying from interstitial myocarditis and by means of the virus produced myocardial lesions in mice. On or about the sixth day after innoculation with the virus, small necrotic foci appeared in the myocardium with monocytic infiltration of the surrounding areas. Three days later in addition to the early inflammatory changes, necrosis became more extensive and fibroblasts began to appear. Calcification was very common in the necrotic foci after the twelfth or thirteenth day. These authors found that if a mouse survived beyond the twelfth day it usually recovered completely. During these experiments one of the laboratory technicians developed signs and symptoms of cardiac disease with a raised blood sedimentation rate and electrocardiograph changes. He recovered and was well again two days later.

Recent reports indicate that the Group B Coxsackie viruses may cause intra-uterine or neonatal infection

manifested in newborn infants by clinical and pathologic evidence of acute myocarditis.

In 1952 during an epidemic of Bornholm disease in Johannesburg, of the ten babies with myocarditis, six developed circulatory collapse and died (Javett et al., 1956). Strains of Coxsackie virus B-3 were recovered from the faeces of the surviving infants. Lesions resembling those caused by a Group B Coxsackie virus were seen in suckling mice injected with suspensions of brain prepared from each of two babies who died.

Montgomery and his colleagues (1955) reported three newborn children in the same maternity home who developed simultaneously an acute febrile illness with no localised findings. The mother of one of them had been febrile previously. Two babies recovered after one week. The third died. Histological sections showed an extensive myocarditis. Foci of inflammation were also found in the adrenals and in the pleurae. Coxsackie Group B type 4 virus was isolated from one of the newborns who recovered, and from the caecal content and from the faeces of the newborn who died. The mother who suffered from a febrile illness before the birth showed type

specific antibodies in her blood three months later.

In 1955, during an epidemic of "summer grippe" among adults in Amsterdam, four fatal cases of myocarditis in newborn infants were studied (van Crevald and de Jager, 1956; Verlinde et al., 1956). The clinical diagnosis of myocarditis was confirmed by electrocardiographic changes during life and the demonstration of acute interstitial myocarditis at autopsy. Strains of B 4 Coxsackie virus were recovered from the heart muscle of each patient and in one instance from the brain.

Two similar cases were encountered in Boston (Kibrick and Benirschke, 1956), Coxsackie virus B 3 and B 4 being isolated.

Cardiac complications of infection by Coxsackie viruses in older children and adults have not been reported frequently but may have been overlooked. Coxsackie B 2 virus was recovered from the faeces of a five-year old boy in Ohio who had acute myocarditis and in whose blood a rising titre of neutralising antibody against the virus was subsequently detected (McLean et al., 1957). Recently two cases of "benign pericarditis" were reported, one associated with a B 4 strain (Fletcher and Brennan, 1957), and another

with a B 5 strain (Weinstein, 1957). Coxsackie virus B 5 was recovered from the stool of a thirty-month old boy with subacute myocarditis, and an associated increase in neutralising and complement-fixing antibodies against this agent was detected (Varcasia and Castelli, 1957).

In four cases of unexplained heart failure in newborns reported by de Jager (1957) the heart was pale and spotty on macroscopical examination. Microscopically, focal cellular infiltration and necrosis were found and in the four cases a Coxsackie virus was isolated from the heart muscle.

In most series of cases of myocarditis, the influenza virus comes high in the list of aetiological factors. According to Kirch (1927), Schmorl (1919) was the first person to refer to myocarditis in patients dying in the influenza epidemic in Europe in 1918. The myocardial changes in infections with haemophylus haemolyticus were described by Miller and Branch (1923) and De Santo and White (1933). Lichty (1937) reported that myocarditis can be caused by a haemolytic parainfluenza bacillus, but it was Finland et al. (1945) who first reported a cardiac fatality in which the influenza virus was isolated.

An M.R.C. report of 1919 listed the pathological findings in one hundred and fifty-three cases of influenza during the pandemic of 1918 and it was stated that "it is unusual to find a heart in these cases that could be considered normal." In 1958, Silber reported a series of twenty-one cases of myocarditis and two cases of pericarditis, of which six were associated with significant rise in antibody titre for Influenza Virus A and B. However, by no means are all observers agreed on the frequency and severity of cardiac complications of influenza. Lichty (1919) and Aldrich (1937) considered post-influenzal cardiac complications to be infrequent, and Opie (1921), Lucke et al. (1919) and Winternitz (1920) were not impressed with the pathologic changes in the heart as a result of influenza. They agree that influenzal infections damage the myocardium but the incidence or significance of the myocardial damage remains unsettled. The likeliest explanation of the remarkable variation in the incidence of cardiac involvement in influenza may be related to the strain differences of the various members of the influenza virus group.

The start of the collection of material of the present

routine autopsy series of cases coincided with the peak of the 'Asian 'flu' epidemic in Dundee in February 1958. Hearts from seven cases (table XIII) diagnosed on clinical or pathological grounds as influenza, were examined, but in no case was virological or immunological confirmation of the diagnosis available.

By far the most common myocardial abnormality associated with influenza was myocardial infarction. In five of the seven cases infarction of the right ventricle had occurred and in two of these the left ventricle was also involved. This remarkable preference for the myocardium of the right ventricle was no doubt related to right ventricular hypertrophy and the subnormal $\frac{LV + S}{RV}$ weight ratios which were present in all but one of the influenza patients of this series. In one case gross atheroma of the coronary arteries was present and in the others minimal to moderate coronary intimal thickening was noted. However, the frequency of relative myocardial hypoxia in patients with influenzal pneumonia must be related to the poor gaseous exchange and consequent hypoxia from diseased lungs, and a reduction in the number of circulating erythrocytes as a result of the massive haemorrhagic type of pulmonary reaction to the influenzal virus. In the acute phase a

further factor in the production of relative myocardial hypoxia is the hypotension induced by toxaemia and diminished circulating blood volume, a factor further worsened once the right side of the heart has begun to fail.

In two of these cases (N 3393 and N 3411) focal infarction was seen in myocardium in which there was a diffuse chronic inflammatory cell infiltration. Lymphocytes, plasma cells and macrophages were present in the myocardium. Areas of myocardial cell degeneration tended to be focal and were related to areas of infarction. However, the differentiation between myocarditis and myocardial infarction was by no means clear cut in this case. This may also be true of the interpretation of electrocardiograph abnormalities seen in the course of influenzal attacks.

In the myocardium of a supposedly healthy man who died two hours after being run down by a "careless driver", and in that of a man who died of multiple injuries within two hours of a factory accident, diffuse myocardial infiltration by plasma cells and lymphocytes was seen. The

victim of the car accident was killed too recently to qualify for inclusion in the routine autopsy series but the sections from the heart of the other patient (N 3428) were extensively studied. The infiltrate consisted of lymphocytes mainly but plasma cells, macrophages and occasional polymorphnuclear leucocytes were also seen. Only a few inflammatory cell foci were present, more commonly the infiltrate being scanty and diffuse. An oedematous looking interstitium was seen in some sections but these changes were by no means definite.

Efforts were made to find out if either of these men had been unwell in the month before their accidents. Unfortunately, neither of them was married and no valid conclusion could be drawn from the information received from the landlady of one or the employer of the other. They had not consulted their doctor in the month before their accidents. The man who died following the factory accident, was admitted to hospital towards the end of the 'Asian 'flu' epidemic of 1957-58 in Dundee, but the car accident patient was killed in the early winter of 1960.

However, it is of considerable interest that two men suffering accidents as a result of a known factory

hazard and the action of a careless driver did in fact show evidence in their myocardium of chronic inflammation which may well have been primarily or secondarily related to their accident proneness. The first patient (included in the routine autopsy series) may well have been convalescing after influenza, but there is less evidence (other than histological) that influenza was causally related to the myocarditis seen in the second.

There seems no doubt that myocarditis can occur in the course of influenzal infection. The incidence and severity of such a myocarditis are not invariably related to the severity of the attack (Walsh et al., 1958) but they are probably dependent upon the type of influenza virus involved. On the other hand the severity of the attack may well be an important factor in the determination of the extent and severity of the lesions of relative myocardial hypoxia. Thus, Brooks (1933) who alone contended that the severity and incidence of myocardial damage was related to the severity of infection, has in the broader sense of "myocardial damage" been proved correct by the limited experience provided by seven Dundee patients dying during the 'Asian 'flu' epidemic of 1957-58.

One of the patients of the routine autopsy series suffered from poliomyelitis in 1951. This patient is discussed in relation to the myocardial changes seen in bacterial endocarditis. It is impossible to deny the possibility that this man's heart was damaged by poliomyelitis for there is little doubt of the ability of the poliomyelitis virus to attack heart muscle.

A microscopic study of thirty-two paralytic cases of poliomyelitis was reported by Marinesco et al. (1957). In fifteen cases, an acute interstitial myocarditis was found. Of these thirteen showed a cell infiltration consisting of lymphocytes, histiocytes, plasma cells, fibroblasts and occasional polymorphnuclears. Perivascular infiltrations were seen especially in the muscle tissue adjacent to the pericardium. In six cases perivascular haemorrhages and thrombosis of the capillaries were present. Most patients were children under fourteen years of age, developing myocarditis in the first week (fourth to sixth day) of the disease and often showing pulmonary complications. Autopsy findings in twenty-seven cases of poliomyelitis were reported by Liszkai (1955). The more severe cases showed acute muscular destruction but the majority showed inflammatory

infiltration without muscular damage. This author considered that damage to the nerves of the heart may contribute to the damage in the heart itself. Histological changes in the hearts of eighteen cases of poliomyelitis were described by Zhukova (1957) who noted that changes in the ganglia were more pronounced than the myocardial alterations. In only two of the cases did the myocardial lesions merit a diagnosis of myocarditis.

Chemical or Toxic Myocarditis

Many chemical substances by their presence, or indeed by their lack, can produce myocardial degeneration and a reparative type of inflammatory reaction.

Changes in the myocardium and in the subepicardial region characterised by foci of polymorphnuclear leucocytic infiltrations were found in rats during experimental magnesium deficiency (Lowenhaupt et al., 1950). For many years emetine hydrochloride in high doses has been known to be able to produce myocardial damage and every medical student is taught that this drug should never be administered to ambulant patients. Evidence of alterations in

the myocardium occurring after therapeutic doses of emetine have been reported by Dack and Moloshok (1947), and Brem and Konwaler (1955) have described interstitial myocarditis due to this drug.

Another drug highly lethal to entamoeba hystolitica is the substituted pteridine 2 - methylamine - 4 - amino - 6 : 7 - diphenylpteridine. This drug was synthesised and developed by I.C.I. Ltd. (Boon, 1957). It is of interest to note, however, that this amoebicide too has been revealed to be capable of inducing a myocarditis (in albino rats) (Paget, 1957). In Hooded Lister rats, however, a high dosage of this drug failed to produce any morphological change of the myocardium (Experiment A).

The list of minerals and drugs said by Saphir (1958) to be responsible for the production of myocardial damage is formidable; arsenic, quinidine sulphate, quinine, ergotamine, atropine, mercurial diuretics and chloroform have all been reported as causes of electrocardiographic changes. Barbiturates, carbon tetrachloride, sulphonamides and bismuth have been reported to produce histologically demonstrable myocardial changes. He also states

that lead has recently merited inclusion in this list, and Macpherson (1956) adds uranium to the list.

Calcium is an important mineral to muscle in general and its deficiency has been reported (Grundner-Culemann, 1952) to be responsible for muscle necrosis. An excess of calcium was reported (Friedman and Bine, 1948) to result in electrocardiographic changes.

In three cases of the present routine autopsy series, hypckalaemic myocarditis was diagnosed.

Potassium Deficiency

Since 1937 when Schrader, Prickett and Salmon reported that myocardial necrosis occurred in rats on a potassium deficient diet, there has been a growing awareness of the importance of the serum potassium level to the myocardium. It is only relatively recently that with the introduction of flame photometry, speedy and accurate serial serum potassium estimations have enabled clinicians not only to establish a diagnosis of the myocardial abnormality but to do something about it.

The first of the three cases of hypokalaemic

myocarditis of the routine autopsy series was a fifty-one-year old woman (N 3415) who had a history of great tragedy. This woman felt perfectly well until the "Mass Miniature Radiography" campaign in Dundee was launched. Having attended for chest radiography she was informed that a full plate X-ray would have to be carried out. Following this, a minimal right apical pulmonary lesion was diagnosed and she was given a supply of antituberculous cachets ('Pycamisan' - Smith and Nephew). About a fortnight later she started having diarrhoea. She persisted taking the cachets for another three days, but having stopped the therapy the diarrhoea went on. She was admitted to the local fever hospital (King's Cross Hospital) grossly dehydrated, but no abnormality was detected in her chest. No intestinal pathogens and a negative Widal reaction were reported by the bacteriologists. The patient became so ill that a total colectomy was carried out in this hospital on 13th February, 1959, about six weeks after the onset of the diarrhoea. Before and after operation, low serum potassium levels were repeatedly demonstrated (full details of which are given in an abstract of the case notes at Appendix A) and repeated electrocardiographic

tracings showed "typical changes of low serum potassium". Immediately following operation this woman did moderately well but a fortnight later she rather suddenly went into shock, and died about twelve hours later. At the post-mortem examination, the heart, apart from being somewhat flabby, had a normal looking myocardium, endocardium, and pericardium, and the coronary vasculature was healthy. No evidence of a lesion at the apex of either lung was found but a terminal bilateral pneumonia and a left sub-phrenic abscess which had destroyed the left adrenal gland were considered to be the causes of death. On microscopy, the abnormality of the myocardium was extensive but varied. Only a few myocardial cells of any one microscopic field were obviously necrotic (fig. 126) and in many areas no myocardial cellular necrosis was seen. However, in abundance in relation to the necrotic cells and rather scanty in many other areas was a principally mononuclear cellular infiltrate. Few neutrophil polymorphs were seen. The macrophages were not of the cardiac histiocyte of Anitschkow morphology, but lymphocytes and plasma cells were recognised. Little evidence of reticulin damage was seen and in this one case no fibroblastic or fibrocytic activity was seen.

The appearances were those of a primarily interstitial myocarditis occurring in a patient in whom biochemical estimations had proved a fluctuating hypokalaemia in life and electrocardiogram tracings showed "typical hypokalaemia changes". No organisms were demonstrated in the myocardium and the paucity of neutrophil polymorphs tended to discount the possibility that the myocarditis was secondary to the subphrenic abscess.

Two other cases in this routine autopsy series, a seventy-year old male (N 3398) and a thirty-six-year old male (N 3414), at autopsy were found to have apparently normal hearts, but on microscopy a light inflammatory cell infiltration of the myocardium was found. Plasma cells, lymphocytes and macrophages were found mainly perivascularly but in some places as a diffuse infiltrate among myocardial fibres in which no evidence of necrosis was found.

The first of these two cases, an elderly man, was admitted moderately dehydrated having had a mild diarrhoea for about a week, after a bout of vomiting. During this time he had eaten almost nothing. Following a barium enema, adult Hirschprung's disease was diagnosed and serum potassium levels were reported as 4.5 mEq./L. and 3.45 mEq./L., twenty-four

days and fourteen days before his death. The other patient, the thirty-six-year old male (N 3414), suffered from a severe and persistent diarrhoea for a month before he was admitted to hospital. A terminal colostomy was performed after laparotomy at which acute ulcerative colitis was diagnosed. He died twelve hours after this operation, no serum potassium estimation having been carried out.

Positive evidence of hypokalaemia in the first of these two cases is based on one low normal and one subnormal serum potassium estimation. In the second ulcerative colitis case there was no biochemical evidence of hypokalaemia. However, the clinical history of diarrhoea and anorexia, and the clinical findings of dehydration, muscular weakness and apathy are suggestive of potassium lack, and raise the probability of this factor being related to the inflammatory cell infiltration of the myocardium in which, however, no evidence of necrosis was demonstrable.

Discussion

Hypokalaemia in man can be defined as a serum potassium level of less than 3.5 mEq./L. of unhaemolysed blood.

In a clinical survey of fifty hypokalaemic patients, Surawicz and his co-workers (1957) found that in most cases there was an average of three potassium depleting factors in each case. Inadequate diet accounted for 84% of the cases. Infusion of potassium-free solutions was a factor in 52% and vomiting had occurred in 46%. Suction and gastro-intestinal fistulas accounted for 24%, and diarrhoea was a factor in 24%. Twenty per cent of the patients suffered from renal disease and in 10% prolonged steroid administration had occurred. Diuretics had been given in 8% and insulin in 2%.

In the first of the three cases (N 3415), four factors contributed to hypokalaemia. Inadequate intake, diarrhoea (due to ulcerative colitis), energetic, early potassium-free infusion to correct the dehydration and steroid therapy, all contributed to the production of a hypokalaemia, which once established, proved extremely refractory to treatment.

Whether the antituberculous drug was directly responsible for the production of the acute ulcerative colitis is difficult to decide. It would seem to be highly improbable that there was no connection between the two in spite

of the fact that the cessation of drug therapy caused no remission of the diarrhoea.

In the other two cases in which hypokalaemia has been inferred rather than proved, the low potassium state could well have been produced by diarrhoea and a low potassium intake.

Most of the work done in studying myocardial changes occurring in potassium deficiency has been experimental. Follis in 1942 produced cardiac and renal lesions in rats by a diet low in potassium content. At fifteen days with a binocular loop, tiny opaque greyish areas were seen beneath the epicardium, and by six weeks the lesions could be detected with the naked eye. The heart was found to be hypertrophied. The earliest microscopic change he noted to be loss of striations of the individual muscle fibres (seen after eight days). The hyaline fibres then lost their affinity for eosin and as the fibres underwent necrosis nuclear shrinkage and an emigration of leucocytes occurred. Follis never saw mural thrombosis and healing occurred by fibrosis. Even late on when extensive fibrosis had occurred, occasional early type lesions were still seen to appear. The potassium content of the heart

muscle of these animals was 35% lower than normal controls.

Degeneration and death of muscle fibres, phagocytosis of necrotic material, and collapse of the supporting stroma without destruction of the connective tissue framework were the features noted by Macpherson (1956) in his paper on potassium depletion in rats. He emphasised the absence of capillary ingrowth and of fibroblastic response. He also was unable to confirm that polymorphs were seen in these lesions. At the early stage, after about one week of potassium depletion, some swelling of the muscle fibres was noted and there was a gradual loss of striation. The nuclei then underwent karyolysis and it was noted that some of the neighbouring fibres contained vacuoles which stained for neither glycogen nor fat. Soon after the eighth day or simultaneously with the loss of striation, cells accumulated round the affected fibres. These were mainly macrophages. Only occasional polymorphs were noted. There was a remarkable absence of collagen formation as the lesion progressed. Phagocytic cells disappeared from the eleventh day onwards and collapse of the reticulin framework occurred. In the

larger lesions, collapse was delayed or partial, resulting in an open acellular network. The oedematous separation of muscles was striking. The other feature which was prominent at this stage in these larger lesions was the presence of small irregular muscle fibres with prominent closely set striations, near the edge and sometimes in the centre of the collapsed stroma. Gradual disintegration of the reticulin occurred and strands of the staining reaction of collagen appeared. Sometimes the reticulin and collagen could be seen in the same fibre and Macpherson suggested that this might represent a conversion of reticulin to collagen.

By giving potassium to some of these depleted rats the myocardial lesions healed in four days to ten weeks, depending on their size. Dense scarring was never seen. Examination of hearts up to four months after the potassium lack was corrected suggested that these lesions ultimately disappear. A striking feature of the hypokalaemic lesion was the accumulation of glycogen in damaged muscle fibres. The most extensive changes were seen in the subendocardium, and the areas most severely involved were in the papillary muscles and trabeculae. The

lesions never involved the endocardium, and mural thrombosis was not seen. Macpherson noted that the structural changes were similar to those produced by diphtheria toxin, mercury, and uranium.

In Experiment B (page 348) an attempt to induce hypokalaemia in rats by the administration of the cation exchange resin, Resonium "A" (Bayer) was successful but no myocardial lesions resulted from the mild hypokalaemic levels produced.

In Experiment C (page 352) attempts to produce hypokalaemic myocarditis by adding chlorothiazide to the drinking water, and by implanting tablets of desoxycorticosterone acetate or giving cortisone by injection were more successful. Significant falls in serum potassium levels were achieved and focal scarring of the myocardium was produced. No "chronic myocarditis" was produced. The appearances were those of healing and healed lesions following acute parenchymatous damage. Chlorothiazide alone failed to produce a hypokalaemia.

In the first case under consideration, the serum potassium levels fluctuated from 2.2 mEq./L. to 5.5 mEq./L. Only in the last week was the hypokalaemia relieved by

energetic therapy. Thus if the results of the experimental work quoted can be applied to the histological findings in this case, the pattern seen was that of the healing stage.

There is no mention in the case notes of this unfortunate patient to suggest that she was ever in cardiac failure. Similarly there is no indication that the other two patients of this group were in failure. In the case of the elderly woman, however, this may be an error of omission rather than a negation of decompensation. Nevertheless, it is difficult to estimate the role of the myocardial involvement as a cause of the death of this patient. A subphrenic abscess which had destroyed the left adrenal gland, and a terminal bronchopneumonia were seen at autopsy and it is likely that the combination of factors leading to this latter final catastrophe included the hypokalaemic myocarditis.

In both of the other patients it seems less likely that the myocardial changes made any significant contribution to the final outcome.

Noradrenaline

There seems no doubt from clinical and experimental (Szakacs and Cannon, 1958) work that noradrenaline can cause severe myocardial damage.

It may be that the pathological changes induced by noradrenaline are the result of an excessive vagotropic action. However, it seems that the substance is one among others required for the transfer of energy phosphate bands to the contractile proteins of myofibrils. A greater than physiological amount of noradrenaline may carry the dissociation of actin and myosin to an irreversible point with destruction of the contractile elements.

In spite of this, however, it should be appreciated that it is in the very cases in which noradrenaline is used therapeutically that focal ischaemic myocardial lesions are most likely to occur. Any patient in prolonged hypotension, especially if previously hypertensive, will develop a series of focal ischaemic lesions which the unwary may ascribe to the noradrenaline.

In the present routine autopsy series, two men aged

thirty-six years (N 3405) and aged fifty-seven (N 3495), were given noradrenaline by intravenous infusions. The extensive myocardial degeneration that was seen was the result of relative myocardial hypoxia, infarction in these cases being the cause for the therapeutic use of noradrenaline rather the result of it.

In cases of shock due to myocardial infarction, this observation may be obvious. However, it is as well to recollect that the degenerative changes which were produced experimentally by Szakacs in no way differ from the myocardial changes following prolonged shock (Melcher and Walcott, 1951). The evaluation of the role of noradrenaline will always be difficult in view of the fact that the experimental lesions it produces are similar to those produced by the clinical state for which the drug is used.

Uraemic Myocarditis

Two of the cases of myocarditis were patients in whom an elevated blood urea level was estimated. The first of these was a sixty-three-year old woman (N 3416) who was admitted with a hemiplegia and was found to have

a renal infection. At post-mortem her hemiplegia was found to be due to left internal carotid artery thrombosis which had resulted in a massive left cerebral softening. An acute pyelitis and cystitis were demonstrated, as were a broncho-pneumonia and pulmonary embolus. Her blood urea level was 90 mgm./100 ml. on the one occasion on which it was estimated and at autopsy no abnormality of the heart was noted apart from a stickiness of the adjacent surfaces of the pericardium and a slight increase in the amount of pericardial fluid. On microscopy an early acute fibrinous pericarditis was found with an infiltration by polymorphs which in places were seen in the myocardium to about one-third of its depth. No myocardial degeneration was demonstrable.

The other case was a sixty-five-year old woman (N 3423) who, three years previously, had undergone a choledocho-duodenostomy and partial cholecystectomy for gallstones. She remained well until her final illness when she suffered acute right-sided pain and jaundice. She survived only three days after her final admission to hospital where she was found to have an extrarenal uraemia (blood urea 106 mgm./100 ml.) and a grossly dilated biliary tree

with calculous obstruction of the common bile duct. At the post-mortem examination a chronic cholangitis was seen. The heart was markedly infiltrated with fat and the myocardium was pale. Microscopically a principally mononuclear cellular reaction was present in the myocardium but in some areas there was a fine fibrosis which was reticular in distribution. Some myofibrillar degeneration was seen subendocardially in the left ventricular myocardium but no areas of frank necrosis were present. No pericardial abnormality was noted.

Acute fibrinous pericarditis occurs in about fifty per cent of cases of chronic renal failure (Wacker and Merrill, 1934) and occasionally as in the former of the two cases reported from this routine autopsy series, the adjacent myocardium was infiltrated by acute inflammatory cells (Langendorf and Pirani, 1947).

The second of the two cases, however, poses many problems. The inflammatory cell infiltration may have been strictly related to the uraemic state but may well have resulted from the hypercalcaemia (Friedmann and Bine, 1948) which is so commonly associated with elevated

blood urea levels. However, as will be seen from the case notes and summary, the manner of this woman's death was by no means clear and it may be that the myocardial changes were related not to the uraemia present but an electrolyte upset.

Isolated Myocarditis

Two types of isolated myocarditis are recognised, Fiedler's myocarditis and giant-cell myocarditis. These two pathological entities may in fact be variants of the same disease.

Fiedler's own description for the disease which now bears his name was "Interstitial Myocarditis". However, Schmorl (1919) who studied the hearts Fiedler described, noted extensive parenchymatous changes with necrosis of heart muscle fibres and inflammatory cell infiltration. Many muscle giant cells were described.

It was Sellentin (1904) who first used the term "Isolated" myocarditis, because he considered that in this

disease the only lesions seen in any other viscus are those resulting from embolism from detached fragments of endocardial thrombus. Tesluk (1956) complained that this was a bad term as frequently the myocarditis is associated with lesions in other organs or tissues notably in the lungs and lymph nodes. However, some authors (for example Collyns, 1959) state that this disease can be confined to the heart.

In Biggart's (1950) opinion the disease, though rare, has probably been overlooked and is not so uncommon as the paucity of cases in the literature would suggest. In the last six years in this Department of Pathology only one example of Fiedler's Myocarditis has been seen at autopsy.

A variety of aetiological agents have been suggested. Some authors (Jonas, 1939; Magner, 1939; and Miller, 1933 are cited by Biggart) describe a granulomatous type of lesion simulating the granulomata of tuberculosis, syphilis or sarcoid whereas others have suggested that the more acute looking lesions may represent the result of a virus infection or a hypersensitivity reaction. Thus it may be that a number of aetiological agents can produce a heterogeneous group of pathological changes in a group of rare

diseases still to be sorted out.

A case of granulomatous myocarditis associated with a thymoma in a seventy-five-year old woman was reported by Langston, Wagman and Dickenman (1959). They found two similar cases in the literature. At the other end of the life span giant cell myocarditis has been reported in an infant (Goldberg, 1955).

Summary

Myocarditis is a not uncommon pathological finding in autopsy material, if the myocardium is given more than a cursory examination. It is a disease which is probably responsible for considerably more morbidity than mortality. Of the patients of this series in whom myocarditis was diagnosed, only in two (the patient with pyaemic abscess of the myocardium, and the elderly woman with hypokalaemic myocarditis) was it considered that the myocarditis contributed significantly to the cause of death. In these and some of the other cases (as has been discussed on page 154 to page 157) myocarditis may contribute to the weighing down of the relative myocardial hypoxia equation as one of the striking features

of this series was the apparent susceptibility of myocarditic hearts to hypoxic change. This was particularly noticeable in the influenzal group of cases.

CHAPTER EIGHT

Tumours of the Heart.

In no case of this series was a primary tumour of the heart encountered. On the other hand, it was a little surprising to find secondary involvement of the heart in over sixteen per cent of the cases of carcinoma.

From a survey of the literature it appears that metastatic tumours of the heart (and pericardium) are by no means rare. It would be unfair to say that metastases in the heart will be found in as many cases as it is searched for, but from a comparison of the present series and the one hundred and twenty-five post-mortem examinations carried out before embarking on this present project, in my own experience the incidence of carcinoma of the myocardium and epicardium is approximately proportional to the number of blocks of the heart taken for histology.

Secondary Carcinoma

In twenty-four patients of the routine autopsy series, carcinoma was diagnosed (table VI). The most common pri-

mary site was stomach (five cases); other sites were pancreas (three cases), rectum (three cases), colon (three cases), cervix uteri (two cases) and bronchus, prostate, breast, bladder, body of uterus, adrenal, oesophagus, and testis (one case of each). Secondary tumour was seen in the myocardium from four of these twenty-four cases, the primary sites being cervix uteri, breast, and pancreas (in two cases).

The patient in whom carcinoma of the cervix was diagnosed was found to have local extension of tumour and metastases in the abdominal lymph nodes. Small metastases were found in the heart. The woman with breast carcinoma had metastases in her vertebrae, pleura, pericardium and heart; and two of the patients in whom carcinoma had taken origin from the pancreas, showed widespread metastases.

Of the twenty cases in whom no secondary cardiac deposits were found, twelve showed evidence of local spread only. Of the remaining eight cases, three showed evidence of only (two cases) peritoneal, or only (one case) lymph node involvement. In the remaining five cases, the peritoneum and liver contained tumour in

one case, the liver and lymph nodes were involved in two others, the liver, left ovary and lymph nodes were involved in the fourth case and in the fifth a seminoma of testis had metastasised widely.

The incidence of autopsied cases of malignant disease in this series is about normal from this hospital, but it is perhaps dangerous to enlarge on the statistical significance of a series of only twenty-four cases. Nevertheless, from these figures some tentative generalisations may be made.

In this series secondary tumour was recognised in the myocardium and epicardium macroscopically in one case (N 3533) and suspected on the epicardial surface of the heart of the sixty-three-year old man (N 3475) who died of a carcinoma of the pancreas with generalised spread. The myocardium of this patient and that of the other two patients (N 3474 and N 3465) in whom microscopic examination revealed secondary myocardial carcinoma, was described at autopsy as normal, in spite of the fact that many blocks were examined. Epicardial involvement was confirmed microscopically in the cases in which it was suspected macroscopically

These tumour deposits are frequently small, easily missed on naked eye examination, and often situated in the myocardium of the right ventricle. In one of these four cases (N 3533) secondary tumour was seen exclusively in the myocardium of the right ventricle and right side of the septum. In case N 3475, only the right ventricle contained secondary foci of carcinoma. In another case (N 3474) although tumour deposits were seen microscopically in the left ventricular wall they were more numerous in the right myocardium. In the fourth case (N 3465), in whom the cardiac tumour deposits were least in number and smallest in size, the secondaries were seen only in the left ventricular myocardium.

An attempt was made to correlate the presence of secondary deposits of carcinoma with the clinical signs and symptoms referable to the cardio-vascular system. It certainly appears that congestive failure is more common in cases in which the heart is involved than when it is not, but in an assessment of this problem, on looking through the notes of these patients it soon becomes obvious that there is more to be considered than the presence or absence of tumour within the ventricular

myocardium. Patients with secondaries in their hearts represent a special group in whom there is little resistance to the invasive properties of their tumours, as a consequence of which they are in general more anaemic, wasted and ill, than those in whom an attempt at localisation of their malignant growth has been more successful.

In one case (N 3475) the patient's breathlessness, loss of weight, and generalised anasarca were thought to be due to a carcinoma of bronchus or oesophagus. Auricular fibrillation was noted clinically and the significance of this abnormality of rhythm was accentuated by the fact that on a hospital admission five months previously the patient was noted to be in normal rhythm. At autopsy, a carcinoma of the pancreas was found to have metastasised to the liver, adrenals, lungs and lymph nodes. Only on microscopy were foci of well-differentiated adenocarcinoma found in the myocardium which I described as macroscopically normal. As can be seen from figs. 51 and 52, the myocardial involvement is considerable in the right ventricle and must have been macroscopically visible. The degree of differentiation of these cardiac secondaries from a carcinoma in the pancreas, is striking, as is the stromal reaction. These

were features noted in the other secondary deposits and in the primary tumour itself. No atrial secondaries were found in this small heart in which the coronary vasculature was almost entirely free of atheroma.

The microscopic and diffuse infiltration of the secondary carcinoma of case N 3474 is seen in fig. 53. The primary tumour was a poorly differentiated carcinoma of the breast which had metastasised widely. Clinically the patient was found to be mildly hypertensive (150/100 mm.Hg.) and ankle oedema, an elevated jugular venous pressure and an ascites were noted. She was in regular cardiac rhythm. Secondary tumour involved the right ventricular myocardium to a greater extent than the left and foci of tumour were also present on the epicardial surface.

The primary site of tumour in case N 3465 was stated to be the pancreas although a fortnight before death the prostate was removed and reported as carcinomatous. The anaplasia of the tumour was commented upon at that time and at autopsy although an apparently primary carcinoma was found in the pancreas, histologically the similarity of pattern between prostatic and pancreatic growth was

striking. In an attempt to resolve the problem, the acid phosphatase activity of the pancreas tumour was assayed and found to be zero. The acid phosphatase level of this patient's serum was within normal limits in life and from a combination of autopsy and biochemical data, together with a slight preference on histological grounds, it was suggested that the more likely primary site was the pancreas. Within the left ventricular myocardium, small focal (figs. 54 and 55) and in places diffuse carcinomatous infiltrations between muscle bundles (fig. 56) were found in relation to which some myocytolysis was demonstrable. Metastases were also found in the liver, gallbladder, adrenals, spleen and lymph nodes. Clinically this patient was stated to have had breathlessness on exertion which was much worse following his prostatectomy. Occasionally swelling of the ankles occurred.

Five months after pelvic exenteration for carcinoma of the cervix uteri, a woman of forty-seven years (N 3533) died of an ascending bladder infection, broncho-pneumonia and abscess formation. Metastases were found in the abdominal lymph nodes and myocardium. Macroscopically

the epicardium near the apex was thick and nodular and on opening the heart a mass of rather friable reddish tissue (4 x 5 cm.) was found intruding into the cavity of the right ventricle from the right side of the septum. Microscopically this mass consisted of poorly differentiated squamous carcinoma which was apparently growing not only in the myocardium but to a much more spectacular extent within thrombus in the cavity of the right ventricle (figs. 57 and 58). In fig. 59 the reticulin pattern of the tumour is seen to be typically carcinomatous with large groups of cells being partially bounded by reticulin fibrils. This cardiac secondary involvement was seen only on the right side of the septum and in the right ventricular myocardium. No retrospective evidence of cardiac failure was gained from the case notes of this patient.

A process of destruction of the myocardium has been poorly followed in these cases. Evidence of cytolysis in relation to the tumour deposits is commonly seen but in general this feature appears to be of minor importance by comparison with the infiltration of tumour among muscle bundles, causing secondary atrophy of the

myocardium but no massive destruction of tissue. Infiltration between the muscle fibres with subsequent atrophy occurs rather than a frankly necrotic process, unless coronary tumour embolism occurs.

Another feature of note in these few cases is that although there is no doubt that these cardiac cellular aggregates are secondary carcinomatous deposits, there is a surprising lack of mitotic activity in them. There is a cellular pleomorphism which mimics the primary growths but the apparent "quietness" of these cardiac secondaries is quite striking.

Discussion

The myocardium may be secondarily involved by carcinoma by direct involvement, or lymphatic or vascular spread. Neoplastic lymphangitis may occur. If small vessels are the site of lodgement of tumour emboli, miliary infarction may be seen without the formation of gross metastatic development. Single, or more commonly, multiple metastatic nodules may develop in the myocardium by extension from secondarily invaded lymphatics or by haematogenous dissemination. Occasionally a diffuse infiltration of the myocardium occurs. When the

endocardial surface becomes distorted by underlying tumour, as in one of the cases of this series (N 3533), endocardial thrombosis may occur in which tumour growth luxuriates. Surface implantation on the endocardium is probably rather rare. Valvular involvement is very rare. Coller and his colleagues (1950) believe that pre-existent valvular damage is a requisite for tumour implantation. They reported a case in which the mitral valve was involved, the six cases previously reported involving the tricuspid valve in five and the aortic in one - another piece of evidence that the right side of the heart is favoured in the development of secondary carcinoma.

It is of interest that as many as four out of twenty-four cases of malignant epithelial disease of this routine autopsy series showed tumour deposits in the heart, but a more striking aspect of this frequency is that in only five of the twenty-four cases did a cancer fail to metastasise to the heart having escaped the confines of the local tissues and lymph nodes. It would thus appear that if the primary tumour has the invasive properties to spread through the local and regional lymph node barriers, the growth has not far short of a fifty-fifty chance of metastasising to the myocardium. In two of the three cases in

which metastases were so numerous that they were described in the autopsy protocols as "generalised", the heart was involved and in all the twenty-six cases of secondary tumour of the heart, Lothe and Somers (1960) reported, metastatic distribution was described as "extensive". In the series of Ritchie (1941), in ten of the sixteen cases of secondary myocardial carcinoma, the distribution of the metastases was "generalised". Only in one of his cases (carcinoma of the oesophagus) was the myocardium the site of the only remote metastasis. Ritchie stated that such an occurrence is infrequent and quoted that Burke (1934) found in his series of fourteen cases that the heart was never the sole site of metastasis.

It was suggested by Lothe and Somers that a figure such as 19.1% (Young and Goldman, 1954) did not represent the expected frequency of cardiac metastasis in general hospitals, but rather represented the frequency seen in tumour reference centres and long stay hospital cases. The inference of such a statement questioning the validity of a generally high secondary cardiac-cancer incidence is that the longer the patients live, the more likely are they to develop cardiac secondaries. This is true only to a

limited extent. There comes a time in considering a cancer history after which, the shorter it is, the more biologically active is the growth and therefore the more likely is the patient to suffer from metastasis. In general, the patients who have the longest histories are those who either have the least biological activity in their growths, or manage to mobilise their tissue resistance to such an extent that metastatic foci cannot take root or find difficulty in doing so.

From a survey of case reports and papers on this subject, the most common primary site for secondary cardiac involvement is found to be the lung. Forty of the one hundred and nine primary bronchogenic carcinomas of Young and Goldman's series had metastasised to the heart and De Loach and Haynes (1953) found that carcinoma of the lung had directly involved the pericardium and heart in twenty-one per cent of one hundred and five such cases. Other common primary sites are pancreas, oesophagus, breast and skin (malignant melanoma).

Cardiac metastases are usually clinically silent. In the series of Goudie (1955) the correct diagnosis of cardiac involvement was never made during life. In retro-

spect, arrhythmias were commonly found. E.C.G.s taken in fifteen patients were all abnormal, but as Siegel and Young (1933) and others have pointed out there is no pattern pathognomonic of tumour of the heart. In a study on the pathogenesis of arrythmias associated with metastatic tumours of the heart James and Carrera (1959) noted that in a case of bronchogenic carcinoma, a solitary metastasis was present in the left atrium between the two anterior pulmonary veins. The patient had had anginal attacks and variable arrhythmias, and these were ascribed to neoplastic invasion of sympathetic nerves in the atrium, neoplastic invasion of an atrial coronary with thrombotic occlusion and atrial infarction, and direct neoplastic invasion of the atrial myocardium. Quite apart from the fact that specific symptoms referable to the heart may be missed because of preoccupation with the generalised illness of patients with malignant disease, the various signs on which clinical assessment of cardiac function are based may be altered by the underlying malignant process. An enlarged liver, increased jugular venous congestion or peripheral oedema may all result from direct venous involvement by tumour. Of much more significance in the diagnosis of secondary

cardiac tumour is a sudden change of rhythm.

In view of the fact that three of the four cases reported here occurred in, or more extensively involved, the right ventricle rather than the left, it is interesting to note that Benjamin (1939), Prichard (1951), De Loach and Haynes, Lothe and Somers, Mahaim (1945) and Coller and his co-workers noted this same feature. However, Scott and Garvin (1939), Willis (1952) and Goudie stated that all parts of the heart are equally susceptible.

Malignant Lymphoma

The heart is commonly involved in malignant lymphoma (Cohen et al., 1955). In one case of this series (N 3455) lymphosarcomatous deposits were seen in the myocardium and were associated with extensive foci of myocytolysis (figs. 47, 60, 61). This was the only case of lymphosarcoma in the series, the other cases of lymphoma being one of Hodgkin's disease (N 3502) in which myocardial infarction had occurred, and four leukaemia cases (included in table VI).

The one instance of lymphosarcoma in the series occurred in a woman (N 3455) who died in the spring of 1959, aged seventy-five years. She had noted increasing difficulty

with swallowing since Christmas 1958, and was admitted in February because of ulceration between the left faucial pillars. Reticulum cell sarcoma was diagnosed from a biopsy of this lesion. She was ill, anaemic (Hb. 9.66 G/100 ml.) and had a moderate reduction in the number of circulating leucocytes and platelets. Deep radiotherapy proved of no avail and the patient's condition steadily deteriorated. At autopsy the right coronary artery was found to be occluded by firm thrombus but no macroscopic myocardial abnormality was noted other than some degree of atrophy (the total ventricular weight was 152 G.) On microscopy some striking changes were noted. Foci of lymphosarcomatous (the biopsy diagnosis was changed after the autopsy) infiltration were present in the myocardium of the right ventricle and tricuspid papillary musculature. Closer examination of these areas revealed myocardial fibre abnormality. In the area shown in fig. 60 and at higher power in fig. 61 considerable thinning of fibres has taken place and in some areas actual fibre breakdown has occurred in relation to the atrophy. Another feature commonly seen in this heart was focal and mainly right ventricular acute

myocardial degeneration. Frequently these changes coincided with an area of cellular infiltration (fig. 47) but in other areas relatively few cells were noted in a zone in which the degenerative change was particularly severe (fig. 62). Occasional zones of acute degeneration were extensive in the right myocardium (fig. 48). Although the lymphosarcomatous infiltrate could well be partly responsible for the acute degenerative change present it would seem more likely that the direct role of the infiltrate is in the production of the myocardial atrophy. From what has been seen in acute hypoxic degenerative change, the focal coagulation necrosis is more likely to be related to hypoxia induced by the combination of right coronary thrombosis, anaemia, multiple pulmonary tumour deposits, broncho-pneumonia and a prolonged (four day) agonal period of hypotension.

In two of the cases of leukaemia (N 3631 and N 3505, the former myeloid and the latter aleukaemic) both showed evidence of myocardial infiltration (fig. 63). In one (N 3631) there was in addition, frank microinfarction of the mitral papillary muscle. Only mild atheromatous change was present in the coronary vasculature of this

patient but of more moment was the haematological factor, the haemoglobin level being 4.5 G/100 ml.

In the other two leukaemic cases (both aleukaemic) abnormalities of the hearts but no leukaemic infiltration were found. In one, a sixty-four-year old woman (N 3406) acute infarction, acute hypoxic degeneration and "glycogenic" degeneration were found in the left ventricular myocardium. This patient had normal coronary vasculature but was grossly anaemic (Hb. 3.8 G/100 ml.) The other case of aleukaemic leukaemia was a forty-five-year old man (N 3576) who was admitted in what was thought to be congestive cardiac failure. He was found to be suffering from cryoglobulinaemia and at post-mortem examination was found to have an extensive tissue proteinosis. The auricular myocardium was extensively involved as were both kidneys. Attempts to demonstrate amyloid substance failed. Only the faintest metachromasia was noted and the nature of this proteinous infiltrate is not known. The patient was markedly anaemic and in the opinion of Dr. H.B.Goodall who studied the case extensively, the marrow smears were diagnostic of aleukaemic leukaemia.

Myocardial infarction, recent and old, was also the

immediate cause of death in the one case (N 3502) of Hodgkin's disease in the series. Coronary atheroma was gross but other factors tending to worsen the degree of relative myocardial hypoxia were a pneumonia, pleural effusion with left pulmonary collapse, and Paget's disease of the skull. No evidence of infiltration of the myocardium or pericardium by Hodgkin's tissue was seen.

Discussion

Of nineteen lymphosarcoma and reticulum cell sarcoma cases, Young and Goldman (1954) found that seven had metastases in the heart. In another series reported by Nabarro (1953) cardiac involvement was found in four out of nine instances of reticulum cell sarcoma, and in one case, only histological evidence of tumour was obtained; four of twenty-seven instances of lymphosarcoma and lymphatic leukaemia likewise showed gross cardiac lesions. Microscopic changes were seen in two additional cases. Of the twenty-four cases of Hodgkin's disease included in the report four showed macroscopic involvement and one microscopic involvement only.

In the various forms of leukaemia the heart and pericardium are quite frequently involved (Aronson and Leroy, 1947). Acute myeloid leukaemia is said to be the most common type to produce myocardial infiltration, and the overall incidence of cardiac involvement is stated to be between thirty and forty per cent. Kirshbaum and Preuss (1943) found the heart involved in thirty-four per cent of their one hundred and twenty-three cases, and Saphir (1958) found leukaemic infiltration in thirty-four hearts from ninety-five cases of leukaemia.

In studying the incidence of secondary cardiac involvement by lymphosarcoma, reticulum cell sarcoma and leukaemia, problems of classification and nomenclature soon intrude. It is for this reason that this group has been considered under the general title of "Malignant Lymphoma". In addition, on reading reports of leukaemic hearts it is frequently difficult to decide if an adequate distinction has been drawn between simple leukocytic infiltration and infiltration by malignant cells. The histological features of reported cases of malignant lymphoma are only occasionally precise in so far as the description of the infiltrate is concerned. In Nabarro's paper the heart of Case I (reticulum cell sarcoma) is described as

"microscopic examination of the heart showed that there was some infiltration", and "the myocardium was severely damaged". These changes are illustrated but it is difficult to say of what exactly the infiltrate or the damage consist. The figure captions do not help. In the other two cases of which details are given, the microscopic changes of the myocardial fibres are not given.

There has been little attempt to prove that secondary neoplastic involvement of the heart is in itself able to produce cardiac failure. A rhythm upset induced by involvement of the conducting system may well embarrass the heart, but a contributing factor must also be the direct atrophying action of foreign tissue within the myocardium.

In this series the extensive myocardial damage seen in cases of malignant lymphoma has been brought about by the hypoxia of the anaemia that occurs in patients suffering from any one of this group of diseases.

Conclusion

The reported incidence of myocardial metastatic involvement in cases of malignant disease varies from as low

as two per cent to as high as twenty-one per cent. The higher incidences of some authors may be due to a predominance of the particular types of neoplasms in which cardiac metastases are most frequent. However, it would appear that much of the difference is accounted for by the variation in the extent to which the heart is examined.

The diagnosis of cardiac involvement in malignant disease will always be extremely difficult but from the now numerous case reports on this subject it would appear that the likeliest clinical signs are unexplained heart failure, often of sudden onset and intractable nature, or sudden disturbances of rhythm.

Neoplastic invasion of the heart occurs more frequently than has generally been realised and merits careful consideration in the differential diagnosis of intractable cardiac failure.

In carcinoma the biological activity of the tumour and the ability of the regional nodes to confine the growth appear to be more important as factors in the development of secondary cardiac cancer than any unsuitability of the environment of the tissues of the heart.

In a survey of the one hundred and twenty-five subjects of this routine autopsy series, in twenty-four the diagnosis of carcinoma was made. Secondary carcinomatous deposits were found in the myocardium of four of these patients.

In six cases the diagnosis of malignant lymphoma was made. In all of these extensive myocardial changes were seen, the myocardium of the one patient with lymphosarcoma and that of two of the four with leukaemia showing infiltration by primitive cells. However, the outstanding and extensive myocardial damage noted in all six patients was hypoxic in origin.

CHAPTER NINE

CARDIAC AMYLOIDOSIS.

The last decade has shown that primary amyloidosis is by no means as rare as has been generally supposed. In a paper on cardiac amyloidosis, Benson and Smith (1956) reported five cases and noted that only ten cases had been reported by 1930; this number had risen to forty-eight in 1945 and to seventy-one in 1950.

Fourteen years after the original description of "lardaceous disease" by Rokitansky (1842), Wilks in a paper "Cases of Lardaceous Disease and Some Allied Infections", described two cases (of thirty-six presented) in which the diagnosis could be classified as "Primary Amyloidosis". However, it was not until 1929 that Lubarsch reported three such cases and suggested the criteria for their recognition.

In considering cases of amyloidosis of the heart in the literature, it is possible to recognise two groups:
(a) those in which amyloidosis was localised principally in the heart, and
(b) those in which the heart was only one of many sites affected by amyloidosis.

Present series

In the routine autopsy series two cases of cardiac amyloidosis and one case of "myocardial proteinosis" have been encountered. The first patient with cardiac amyloidosis was a male aged eighty, (N 3445) who had a thirty-year history of dyspepsia. He was admitted to hospital with retrosternal pain which had lasted three hours, and died twenty-four hours later from relative myocardial hypoxia. This patient was admitted in shock, in auricular fibrillation, and in congestive cardiac failure, but from the history it seems unlikely that congestive failure had preceded this last episode of relative myocardial hypoxia. At autopsy no macroscopic evidence of amyloid of the myocardium was noted. Coronary atheroma was severe; the right coronary artery was occluded at one point by old thrombus and the anterior descending branch of the left coronary artery was blocked by fresh thrombus. The myocardial changes noted macroscopically were those of healed infarction and focal myocytolysis.

Other points of note in this autopsy were a chest scar overlying a grossly fibrosed pleura and a horseshoe

kidney. It is impossible to deny the likelihood that an empyema in this case years before, produced amyloidosis. However, no evidence of amyloid substance was seen in the liver, spleen or horseshoe kidney, so that the role of the long healed empyema is unlikely to be significant. This argument is strengthened when the histological pattern of the cardiac amyloidosis encountered in this case is discussed.

The other case was a seventy-six-year old man (N 3752) who for years had been unable to walk up any steep gradient without stopping many times to catch his breath. He was admitted in congestive failure having had severe chest pains off and on for four days. This patient too had had a long history of dyspepsia. He was in normal cardiac rhythm but a systolic thrill at the apex was noted with a rough murmur which was described as "blowing" in character. At autopsy an extensive broncho-pneumonia, pulmonary embolism, and macroscopic evidence of relative myocardial hypoxia were found. A chronic ulcer was found in the stomach which had been partially resected about nine years previously. A kyphoscoliosis was noted. Macroscopically and histologically no evidence of tuber-

culosis was found and Dr. Todd who performed the autopsy considered that the kyphoscoliosis had a traumatic aetiology perhaps associated with an underlying decalcification. No amyloid substance was demonstrable in the liver, spleen, kidneys and lungs.

In neither case was amyloidosis suspected in the ward by the clinicians or in the autopsy room by the pathologists who performed the post-mortem examinations. Clinically both patients were in failure and according to Higgins and Higgins (1950), heart failure was present in fifty-six per cent of the seventy-one cases of primary amyloidosis they reviewed. However, in both of the cases reported here, relative myocardial hypoxia had been sufficient to cause extensive myocardial changes which may well have resulted in the degree of congestive failure noted, in the absence of any amyloid substance in the heart.

Another feature of primary amyloidosis, macroglossia, was not present in these cases. However, neither a section of tongue nor gum was taken from these two autopsies.

It is impossible to be certain that these two cases are examples of a purely cardiac amyloidosis, but, to the

limit of the extent to which the autopsies were carried out by two pathologists of considerable experience, the likelihood is that these cases are examples of primary or atypical amyloidosis of a mainly, and probably solely, myocardial distribution.

A third case was a male aged forty-five who was admitted with a history of four weeks dyspnoea on exertion. He had noted ankle swelling for nearly a year and complained of recurrent skin sores. On investigation he was found to have a strong circulating cryoglobulin and a diagnosis of aleukaemic myeloid leukaemia was made. After a gradual deterioration the patient died of bronchopneumonia and was found to have abnormal protein infiltrating the walls of the vasculature of the skin, kidneys and auricular myocardium in particular, and almost every other organ in the body in general. The auricular myocardium was diffusely infiltrated with this eosinophil substance which would not accept the metachromatic stains.

Histologically in the two cases in which the amyloid substance was found only in the myocardium, the features were identical. The cardiac stroma was focally involved (fig. 127) and in figs.43, 128 and 156 the higher power

photographs show a very remarkable feature. The amyloid substance is present as a hyaline membrane within the honey-comb-like structure of the reticulin framework of the myocardium. The vessels were not affected.

All the chambers of the heart were affected.

The third case showed a much patchier clumped pattern of infiltration and had no constant relation to the reticulin pattern. The affinity of the proteinous material for Scarba Red was very much less than was true amyloid substance and vessel involvement was striking.

Discussion

The third of the three cases is quite different from the other two in that the protein-like substance is not metachromatic, involves the vasculature particularly, and is seen in organs other than the heart.

The other two cases, however, are typical of the many cases of this group reported in the literature.

The age distribution of primary amyloidosis is wide but most cases occur in the sixth and seventh decades. However, in cases in which amyloid is found only in the

heart, the patients tend to be beyond the age of seventy years. This relation between ageing and cardiac amyloidosis is particularly interesting in view of findings in experimental animals. In the heart of various animals senile tissue changes are comparable to amyloid infiltration. When working with large colonies of inbred mice which were allowed their natural life span, Mühlbock (1956) reported a remarkable incidence of amyloid infiltration and its sequelae among the senile degenerative conditions and the causes of death in certain strains. In 1957, Thung published descriptions of amyloid deposits in various organs of untreated old mice and stated that these lesions increase in frequency and severity as the animals age. In some inbred strains severe amyloidosis is invariably found in old age while in others the findings are slight.

The amyloid infiltration observed in the hearts of senile mice spreads along capillary and lymphatic spaces, surrounds and causes atrophy of muscle fibres and produces a picture such as is described by Josselson et al. (1952) and Hässelmann (1955). In contradistinction from the human condition, however, small and medium sized

arteries were sometimes little affected.

This type of amyloidosis of mice may be dependent upon genetic factors (Heston and Deringer, 1948; Thung, 1957); its incidence can certainly be varied by dietary changes (Heston et al., 1945), but fundamentally it appears to be related directly to age.

Of six hundred and one hearts thoroughly examined from patients with various clinical diagnoses Hüsselmann (1955) found amyloid substance in forty. He found that the severity of involvement was proportional to the patient's age and all but three of these patients were over seventy years of age. It was in this paper that it was pointed out that no sharp differentiation was possible between atypical cardiac and typical generalised amyloidosis.

Seven cases of "atypical amyloid" in the myocardium were reported by Lee and Kaufmann (1957). Their patients were aged seventy-two to ninety-four years and in the myocardium two forms of amyloidosis were seen, a patchy and a diffuse form. Amyloid deposition in other organs was either absent or insignificant in the patients to whose death these authors consider that cardiac amyloid did not contribute.

The aetiological agents of this cardiac amyloid of the elderly could be related to the ageing process or perhaps malnutrition. From the very exhaustive review of the literature by Mulligan (1958), malnutrition appears to have been noted frequently in these old subjects, and he quotes Bock's (1948) findings of a fall in the level of serum albumen in these patients. Bock attributed the changes to failing regulation of appetite and a reduced capacity for synthesis of plasma proteins.

A contributory factor in the two cardiac amyloid cases reported here was a long dyspeptic history in both which may well have resulted in some degree of protein depletion. Experimentally the production of gastric ulcers was found by Hahn and his colleagues (1957) to lead to marked depletion of protein.

Conclusion

Two examples of cardiac amyloid and one of "myocardial proteinosis" (with generalised proteinous infiltration) have been seen in this routine autopsy series.

Cardiac amyloid is a disease seen in aged and more commonly, male subjects. It seems likely that this disease occurs as a result of a minor defect in plasma protein synthesis and protein absorption. A hypoalbuminaemia and a relative or absolute hyperglobulinaemia (of a very small degree of abnormality acting over a long time) may well lead to a leakage of globulin into the tissues and the deposition of amyloid.

CHAPTER TEN

EXPERIMENTAL WORK.

In a consideration of the causation of relative myocardial hypoxia, absolute measurement of the coronary factors can be made at autopsy and of the haematological factors, in life. The myocardial factors are by no means easy to assess, and indeed there is little unanimity on their relative importance.

Human material from the routine autopsy series yielded an abundance of hypertrophied and scarred myocardium and a few hearts in which there was evidence of inflammation. However, in human tissue from a post-mortem series, the combinations of coronary vascular disease, pulmonary disease, anaemia, myocardial hypertrophy, scarring and so on, make the task of elucidation of the relative importance of the individual factors, impossible. By experiment the variables can be controlled. By altering one myocardial factor at a time it was hoped to study the effect of each on the susceptibility of the myocardium to hypoxia.

One possible myocardial factor worth consideration was myocarditis, in view of the finding that in five of the ten

examples of this disease in the routine autopsy series, the degenerative changes of relative hypoxia were seen.

Secondly, as has been seen, the reason for the susceptibility of hypertrophic myocardium to hypoxia is by no means clear and the role of anaemia in its production has recently been called into question. It was considered that hypertrophy and its relation to anaemia should be re-examined.

Thirdly, it was thought theoretically possible that the requirement of the myocardium for oxygen could be varied by inducing various degrees of thyrotoxicosis. However, there is experimental evidence to prove that thyroid given to animals leads to myocardial hypertrophy. This was a further problem worthy of experiment.

Fourthly, a small experiment to study myocardial hypoxic early changes revealed by the electron microscope was carried out.

This project is incomplete. It is hoped to carry out hypoxia producing experiments on animals in whom the myocardium has been made hypertrophic and in animals in whom a myocarditis has been produced. By a comparison of the changes induced by hypoxia in normal myocardium,

in hypertrophic myocardium and in the presence of myocarditis, it is hoped to be able to make an accurate assessment of the factorial value of the grades of hypertrophy and myocarditis.

The results of a series of pilot experiments (A to G) into methods of producing myocarditis and hypertrophy in rats are given. In Experiment H, the induced hypoxic changes in previously normal myocardium are described.

The Animals

Hooded Lister rats from the Rowett Research Institute, Bucksburn, Aberdeenshire were used in Experiments A to G. These animals were mature and varied in age from three to nine months at the beginning of each experiment. At three months they weigh 215 - 280 G. (females) and 290 - 379 G. (males). Fully grown, these animals reach 400 - 600 G., the males being the larger.

The stock at Bucksburn is healthy and in this laboratory no epidemic illness has occurred. A few animals became incidentally ill and a couple of them developed sarcomas.

In spite of its size, the Hooded Lister rat is easy to handle, very benign and almost as easy to inject intravenously as mice.

The basic diet of these animals under experiment was tap water and rat cake diet 86 (North Eastern Agricultural Co-Operative Society Ltd.) The ingredients of this diet are:

Ground wheat	50 parts	Dried yeast	5 parts
Ground barley	25 parts	Salt	1 part
White fish meal	7 parts	Adisco	1 part
Meat and bone meal	6 parts	Dried grass meal	5 parts

The water was changed and the food hoppers were topped up daily so that the animals were able to eat and drink ad libitum. The only supplement was weekly cod liver oil given by soaking a few cubes of rat cake in the oil and placing the cubes in the hopper.

Aim 1.

To produce a standard method of inducing myocarditis.

Experiment A.

Following the report of Paget (1957), that a substituted pteridine, MADP, (2-methylamine-4-amino-6:7-diphenylpteridine), was capable of displacing myocardial fibre cytoplasm and destroying that part of the fibre in which it is concentrated, it was thought that this substance might be useful in the production of myocarditis and the study of the reaction of the degenerating myocardium. The changes reported in the fibres at the edge of the lesions suggested that some disorganisation of the fibres preceded the disappearance of the cytoplasm. Particularly interesting was the appearance of PAS positive material similar to that found by Yokoyama and his colleagues (1955) in areas of myocardial infarction.

M.A.D.P. was synthesised in the laboratories of I.C.I. Ltd., (Boon, 1957) in the hope that its amoebicidal properties could be used therapeutically.

Materials and Methods

On a dosage of 50 mgm. M.A.D.P./150 G. body weight, twice daily for two days, Paget found that "something like 100% of the animals developed cardiac lesions"

(private communication). Four Hooded Lister rats (two female and two male) weighing from 215 - 295 G. were given 50 mgm. M.A.D.P./150 G. body weight twice daily for two days. This substance was suspended in water and given by gastric tube. Four control animals were given only water by gastric tube.

No animals died during the experiment. Two M.A.D.P. animals were killed on the third day, that is, on the day after the last dose of M.A.D.P. was given. Two control animals were killed at this time also. The two other animals on M.A.D.P. were killed on the fifth day as were the two remaining members of the control group.

The organs of all animals were examined at autopsy under ultraviolet light from a high pressure mercury arc lamp.

Some myocardial tissue was fixed in Bouin's solution and blocked in paraffin after double embedding, but additional blocks were fixed in formalin and frozen sections were cut. These were mounted on slides and examined unstained by fluorescence microscopy, using light from a carbon arc.

M.A.D.P. is a bright yellow crystalline substance which in a solid state fluoresces bright yellow. It is poorly soluble in water but such solutions also fluoresce faintly yellow. The compound is soluble in aqueous hydrochloric acid and such solutions fluoresce lime green, as does the solid hydrochloride of the compound and its aqueous solutions (Paget, 1957).

Results.

Macroscopic and microscopic evidence of fluorescence was seen in the stomach, intestine, liver and kidneys of the M.A.D.P.-treated animals. In the heart of the M.A.D.P.-treated animals killed on the fifth day both macroscopic and microscopic diffuse green fluorescence was marked, whereas in those killed on the third day the change was not so pronounced. In no instance did a heart show discrete areas in which myocardial fibres were packed with fluorescent green granules, and in conventionally stained sections, no abnormality was detected in the myocardium of any of the animals in this experiment.

Discussion

In the original M.A.D.P. toxicity trials carried out by Paget, albino rats of a Wistar strain were used. It may be that these were more susceptible to the action of this substance given at a lower dosage, than were the larger Hooded Lister animals used in this experiment.

The fluorescent properties of M.A.D.P. make it an easy substance to detect and there is no doubt that it was absorbed and widely distributed in this experiment. However, the diffuse distribution of the fluorescence in the heart suggests that there was no actual penetration to within the substance of the myofibres, the disorganisation of which was described by Paget as a prelude to the disappearance of the cytoplasm.

Conclusion

The substituted pteridine, M.A.D.P. (2-methylamine-4-amino-6:7-diphenylpteridine) although absorbed and widely distributed, failed to induce a myocarditis in the four Hooded Lister rats to which it was given in high dosage by gastric tube.

Experiment B.

Most of the methods of producing myocarditis by means of electrolyte upsets have been achieved by careful dieting. Since the work of Follis (Follis et al., 1942), experimentalists have been able to produce the myocarditis of hypokalaemia by giving diets low in potassium content and by the administration of adrenal hormones. The dietary method is fraught with problems and it was hoped that a useful method of producing hypokalaemia might be achieved by the use of an ion-exchange resin. Sodium polystyrene sulphonate (Resonium A, Bayer Products Ltd.) eliminates potassium from the gastro-intestinal tract, it restricts the absorption of ingested potassium, and will reduce the potassium concentration in the normal individual. In fact, however, cation exchange resins never take up their full theoretical capacity of the ions of sodium, potassium, calcium and magnesium, (McChesney, 1952). This is to be expected since even under ideal conditions in vitro, they remove only seventy to eighty per cent of their full capacity of ions (McChesney, 1951; Hegsted et al., 1951).

Resonium A is supplied in the form of a finely ground

and pleasantly flavoured powder and can be made into a soft toffee-like substance by mixing with simple syrup (B.P.) When placed in food hoppers it slowly solidifies to a fudge-like consistency easily eaten by the gnawing rat teeth. Rats ate this sweet substance in preference to rat cake so that there was no problem of administration.

The normal human adult dosage of Resonium A is 15 G. three or four times daily. The rats were given 5 G. daily initially. Twenty grams of the powdered resin was mixed with twenty millilitres of simple syrup (B.P.) The mixture was divided into four approximately equal portions, one of which was given to each of four animals.

The only restriction to which these animals were dietarily confined was that their drinking water was distilled.

After the first day the dosage was doubled, each test animal (Rats No. 15, 16, 17 and 18) receiving 5 G. twice per day, for the ensuing fortnight. Finally, the dosage was raised to 15 G. a day by the addition of a third 5 G. dose. This was continued for ten days after which all

the animals appeared well, had maintained their weight and showed no evidence of cardiac or any other disability.

For three weeks the animals were then given no resin but were kept on their distilled water. Following this two (Rats No. 16 and 18) of the four animals were restarted on Resonium A (at 7.5 G. per day) and this was continued for six weeks after which all the animals and the controls were killed. In this way it was hoped to produce a gradation of response in the two experimental groups and to attempt to assess the reversibility of the lesions seen.

During the entire experiment there was not a single death. The controls were given rat cake soaked in 5 ml. simple syrup (B.P.) when the test animals were given their Resonium A.

Results (see table VII)

Biochemical estimation of the serum potassium levels was carried out by flame photometry.

A somewhat surprising finding was the high level of serum potassium in the normal Hooded Lister rat.

This level in intreated rats was never below 6.0 mEq/L. and often as high as 7.5 mEq/L. Hypokalaemia has been defined in these animals as a level of serum potassium below 6.0 mEq/L. and was achieved on these high dosages of exchange resin but neither clinically nor pathologically was any myocardial abnormality noted. An attempt to trace an electrocardiogram on the test animals was made by using the standard machine at maximum sensitivity. Tracings were obtained but no difference between those of the control and test animals was demonstrable.

Conclusion

Although the resin, sodium polystyrene sulphonate, Resonium A (Bayer), achieved a mild hypokalaemia for prolonged periods, neither immediately after that hypokalaemia nor six weeks afterwards was there any histological evidence of myocardial abnormality.

The animals on the high resin dosage thrived, showed no evidence of water retention and their weight charts closely paralleled those of the control animals.

Experiment C.

Chlorothiazide (6-chloro-7 sulfanyl -1, 2, 4-benzothiadiazine-1, 1-dioxide) was introduced by Beyer (1956) as an oral diuretic. Studying the effects of this carbonic anhydrase inhibitor in cardiac and renal diseases Crosley et al. (1960) found that in addition to haemodynamic changes (a decline in cardiac output, and a significant reduction in glomerular filtration rate and renal blood flow), chlorothiazide acts on the renal tubules by enhancing the excretion rates of sodium, potassium, chloride and buffer base. The changes in urinary electrolyte excretion are responsible for the observed increase in urinary pH, as well as increased osmolarity clearances and the resulting water diuresis. Despite such marked increases in the urinary buffer base, only minor changes in the plasma electrolyte concentrations are found with the possible exception of a trend towards hypokalaemia. It was this effect that was aimed at.

The beneficial effect of desoxycorticosterone acetate (DOCA) in Addison's disease is due to its action on the renal tubules leading to excretion of potassium and a retention of sodium ions. It was suggested by Darrow and Miller (1942) that DOCA administration leads to a decrease

in the potassium content and an increase in sodium content of muscle. The increase in sodium ions replaces the potassium ions lost from the fibres.

It was thus decided that another attempt to produce hypokalaemia should be made by allowing rats to drink only distilled water to which chlorothiazide had been added and to implant DOCA (200 mgm.) subcutaneouly or to give these animals intramuscular injections of cortisone (50 mgm. at approximately weekly intervals.) The whole experiment lasted nine and a half months and details of the dates, treatment, serum potassium levels and fate of each animal are shown in table VIII.

Two rats (one DOCA implanted animal on chlorothiazide water, R38, and one animal on chlorothiazide water alone, R42) died. R38 died six months after DOCA implantation and R42 died three months earlier of intercurrent infections. No abnormality was found in the heart of R42.

Serial serum potassium determinations could not be carried out more than once weekly but it is apparent that some degree of hypokalaemia was achieved by the means of

drugs alone. No balance studies were performed. Another regretted fact is that the potassium contents of the myocardium and skeletal muscle were not estimated. Although the biochemical determinations were carried out by me personally, these projects demanded more in the way of the use of biochemical facilities than were available at the time.

Results

Chlorothiazide and DOCA Group (R38 and R39)

In these animals evidence of cardiac muscle damage was found. Fibrous tissue replacement of cardiac muscle was focal. One animal (R38) died six months after DOCA implantation and the other (R39) was killed, three months after implantation but both showed essentially similar lesions, the only difference being that the fibrosis of the myocardium in R39 (figs. 64 and 65) was considerably more cellular than in R38. There was no evidence of an active inflammation.

The appearances were indistinguishable from those following hypokalaemic myocarditis as described by Macpherson (1956). There is no real destruction of the connect-

ive tissue framework but following necrosis of muscle there is collapse of the reticulin pattern or, more accurately, condensation of reticulin and mesenchymal proliferation to produce a focus of scarring similar to that seen following myocytolysis. A very similar pattern is seen in the human heart as a result of diphtheria toxin (fig. 46)

Cortisone with and without Chlorothiazide

Rats 40 and 41 were given cortisone intramuscularly as "cortisyl" (a suspension of cortisone acetate 25 mgm./ml.) and to their drinking water, chlorothiazide was added (1 G. to 120 ml. of distilled water). Rats 44 and 45 were injected with cortisone and allowed to drink only distilled water. There was no significant difference between the groups clinically, biochemically or histologically. The four animals were killed three months after the start of the experiment, having received 600 mgm. of cortisone.

The fluctuations in potassium levels noted in all these animals was striking and no doubt indicative of the relatively brief action of the cortisone acetate suspension

which was given approximately weekly. However, under even this regime, focal cytolytic lesions were found in which reticulin collapse and mesenchymal proliferation had resulted in the production of small scars. The changes were not as extensive as in the "chlorothiazide-DOCA" group. Once again no evidence of polymorph infiltration was present.

Control Groups

Rats 42, 43, and 37 constituted one control group of animals. They were given chlorothiazide in distilled water but no steroids. Rat 42 died nearly three months after the start of the experiment; Rat 43 was killed a week later and Rat 37 was killed three months after that.

Plasma potassium levels were unaffected by the chlorothiazide alone and histologically no abnormality of the myocardium was found.

Finally, four other animals were kept as a control group drinking distilled water only but eating their normal diet - as did the test animals. These animals formed the control group of not only this experiment but also Experiment B. Histologically no abnormality of the myocardium was found in these animals.

Conclusion

The steroid-salts, desoxycorticosterone acetate and cortisone acetate, can induce focal scarring in the myocardium, probably by means of the hypokalaemic necrosis they cause. These steroids were unsuccessful in producing a "chronic myocarditis". They apparently cause parenchymatous damage which is followed by repair but are not responsible for a continuing low grade interstitial inflammation.

Experiment D.

It was hoped that diphtheria toxin might provide in rats, a means of producing a controlled myocarditis. The rat myocardium is considered by the workers in the Wellcome Research Laboratories to be roughly comparable per kilogram with that of the mouse (personal communication) and the diphtheria toxin kindly given to me by these Laboratories was reported to have an LD_{50} per milligram of 3.5 for mice, and 3,500 for guinea pigs per kilogram of animal. In the solution received 1 Unit (1 r dose) was contained in 0.017 ml.

There was considerable delay in the arrival of this toxin. Owing to a misunderstanding the material was sent to the Bacteriology laboratory at Queen's College where it lay unrefrigerated for a week before arrival in this laboratory where, owing to my absence, another ten days elapsed before it was used.

Two millilitres of a suspension of varying dilutions of diphtheria toxin in distilled water were injected intraperitoneally into four rats. The strengths used were 1:10, 1:50, 1:100, and 1:200. No ill-effects resulted and fourteen days later the animals were injected as before. The animals remained healthy and three were killed on the three successive days after the second injection. The fourth was killed six months later.

In none of these animals could any histological abnormality be demonstrated in the myocardium or other organs.

Conclusion

Before use, the toxin, long exposed to room temperature, should have been retested and re-assayed in the

guinea-pig. Not having a microsyringe, I used relatively large injection masses in high dilutions and having failed to inject the whole dose intravenously in the first animal, I had to recourse to the intraperitoneal route. This in itself should not have diminished the toxicity of the large doses to any significant extent.

No valid conclusion can be drawn from this experiment.

AIM 2.

To produce a standard method of inducing hypertrophy.

Experiment E.

Evidence from experimental (Toussaint et al., 1953; Meneely et al., 1953, and others) and to some extent human studies have been accumulating to suggest that salt may play a significant role in the production of hypertension. Hypertensive vascular disease was found by Koletsky (1958) to develop frequently in rats drinking 1% saline instead of tap water over a prolonged period (up to sixteen months).

He found that the animals developed an intermittent elevation of blood pressure rather than a sustained high level. The highest levels were usually observed in the later months of life when the elevation tended to be sustained. This is no doubt related to the frequency with which a glomerulitis was found in these animals. However, the changes responsible for elevated if labile blood pressure occurred before a significant morphological renal lesion could be seen.

Putting salt in the drinking water seemed to be an eminently suitable way in which to produce myocardial hypertrophy as Koletsky found that the cardiac index, heart weight: body weight X 10^{-4}, was elevated in all the animals drinking salt whether they became hypertensive or not. It seemed that not only hypertension had a hypertrophy producing effect, but also the salt itself contributed to the enlargement of the heart.

The complication of vascular disease was a feature seen late on by Koletsky, and is not commented upon by the authors who did not continue the saline-therapy for more than a few months. It seemed that some six to nine months treatment with saline might provide significantly

hypertrophied hearts in which the vasculature was normal.

In previous experiments normal saline or at most 1% saline was used as drinking water. To humans this is barely palatable but strangely enough I have found that 2% saline is by no means twice as bad. Thus, two sets of animals were started off on saline drinking water on 26th January, 1959. The treatment and fates of the animals are given in table IX. Three animals (Rats No. 23, 24, and 25) were given 1% saline and five animals (Rats No. 26, 27, 28, 31 and 34), 2% saline to drink. Within twenty-four hours it was obvious that to rats, 2% saline is well nigh undrinkable. All of the 2% group had lost weight and approximately half the amount of saline drinking water was consumed by those animals by comparison with the rats of the 1% saline group.

The 2% group were then given an hour of normal tap water and returned to their 2% saline. However, after four days of this regime the animals were still losing weight and all were transferred to tap water. Two more animals (R32 and R33) were used to make up the number of those on 1% saline to equal those who had been on 2% saline and were now converted to tap water. It is undoubtedly true to say that these rats on 2% saline

were extremely thirsty after the first day, mildly dehydrated on the second (in spite of one hour's drinking of tap water), more markedly so on the third day, and by the fourth they were too ill to continue the experiment. Only two of the animals recovered. Such an experience makes the reading of reports such as those of Sapirstein, Brandt and Drury (1950), or Toussaint et al. (1953) the more surprising. These authors substituted 2% saline for drinking water; one group (the former) found that these rats developed hypertension but the French workers' rats did not. These variations of saline tolerance and the variability of effect must be related to strain and breed differences.

Rats No. 31 and 34 (subjected to 2% saline for four days - on each of which they had been given tap water to drink for one hour) continued to lose weight precipitously and eight and ten days after the start of the experiment they died. They had each lost over 100 G. in weight and at post-mortem and on histology I was unable to demonstrate any positive abnormality. One must assume that an electrolyte imbalance, induced by the strong saline solution, was unable to be resolved by the normal, physiological mechanisms. However, there was no

confirmatory histological proof of such an electrolyte imbalance.

Another experimental animal which did not last through the whole experiment was R24, one of the members of the 1% saline group. This animal had to be killed six months after the start of the experiment as it became extremely vicious. This was the only vicious animal of over a hundred of this breed of rat I have had in this laboratory. On the evidence of this one animal it is impossible to incriminate saline administration as a cause of this change in behaviour. At autopsy no abnormality was demonstrable other than a mild hypertrophy of the myocardium.

Finally, nine months after the start of the experiment two animals R25 and R26 (that is, one of the group on 1% saline and one from the group that were on 2% saline for four days followed by tap water for nine months) were anaesthetised and given DOCA (200 mgm.) subcutaneous implants. R26 died eighteen days later with an intercurrent pneumonia.

Five months later R25 was again anaesthetised and a large sarcomatous mass was removed from the axillary region.

The animal was grossly shocked after the operation but recovered and was apparently well within an hour or so. However, next day, the wound was found to be gaping, and much blood clot distended the area previously occupied by the tumour. It was decided to kill the animal.

All the remaining animals were killed on 11.4.60, fourteen months after the start of the experiment.

Attempts were made to record the blood pressures of these animals using apparatus of the type described by Byrom and Wilson (1938) with anaesthesia and without anaesthesia on warmed animals. I was quite unable to obtain reproduceable results and could vary the readings at will. Warming and anaesthesia undoubtedly produced lower pressures and there was no difference in response to these procedures in the experimental animals and the controls.

It will be noted that much the highest mortality was seen in this of all the experiments. Animals given saline drinking water have a materially reduced life-span, the principal cause of death being intercurrent infection, especially pneumonia. Of the twelve animals used only

seven of them were killed for no other reason than that demanded by the experiment.

When the animals were autopsied each heart was excised by cutting across the blood vessels at their junction with the heart, opened, washed and blotted dry before being weighed on a balance. The results are detailed in table IX.

Histology of the myocardium revealed corroborative but no absolute evidence of hypertrophy in R23, R25, R27 and R32. The technical problem of measuring fibre thickness in the rat myocardium is made difficult by the problem of arranging blocking, and trimming to ensure a section from roughly the same area in each heart. Fibres vary widely in thickness from one area to another and as in the human material fibre measurement was found to be most constant (or to put it another way, the error of repeated counts was least) in relation to a fixed point within the ventricular wall. In the rat hearts the base of a papillary muscle in the left ventricle was the site at which measurement was attempted. However, often enough this area was not present in the block taken and fibre thicknesses of other areas were measured.

No case of hypertensive vascular disease was seen in this experiment.

Conclusion

The results of this pilot experiment were sufficiently convincing to conclude that the Hooded Lister rat is able to tolerate drinking a 1% saline solution instead of tap water for long periods, although this regime may predispose to intercurrent infection. Sufficient encouragement was gained to suggest that by this method myocardial hypertrophy unassociated with significant vascular disease might be induced in a high proportion of Hooded Lister rats surviving this regime for periods greater than nine months.

Unfortunately not even a tentative conclusion was possible on the question of the ability of DOCA to accentuate the saline effect. One of the two DOCA implanted animals died of pneumonia eighteen days after receiving the implant and the other developed a sarcoma. This animal was operated upon in an attempt to save it but it lost much blood during and after the operation. It survived a day but looked so miserable that it had to be killed the next day. The heart of this animal was

enlarged to no greater an extent than those of the rats on 1% saline.

Experiment F

There is a considerable volume of literature on the production of heart disease by both overactivity and hypofunction of the thyroid gland. Human myocardial studies to assess the role of thyroid disease are complicated by coincidental degenerative diseases of the myocardium and coronary vasculature, and there are still many who doubt whether thyrotoxicosis itself can produce organic cardiac changes (Thomas, 1957).

Thyroid extract has been used by many experimental pathologists to produce hypertrophy of the heart. In this country Sandler and Wilson (1959) in a number of communications have shown this effect electrocardiographically and by direct heart weight measurement. These workers also found that thyroxine produced cardiac enlargement. Triiodo-thyronine has been noted to produce a similar effect (Gemmill, 1958).

An experimental group and a control group of four animals, were matched for sex and size. Two of the experimental group were given 20 µgm. triiodo-thyronine

daily (six days a week for eight weeks) and two were given thyroid extract (thyroid (B.P.) gr. 1 daily) for the same length of time. These drugs were given by gastric tube. The tablets were crushed in tap water and injected down a thin rubber catheter previously passed into the stomach. The control animals were intubated and given tap water. After fifteen intubations, the daily tablets were broken up and given in the drinking water, an attempt having been made to assess the amount of water being drunk by each animal daily so that the tablet could be crushed into this amount, thus obviating loss of triiodothyronine or thyroid, or the use of stale water.

Results

The weight gain of the control group and the experimental group showed no significant difference during the two-month course of the experiment, although the main daily food average intake per experimental rat was 37.6 G while that of the control animals was 30.2 G.

The eight rats used survived until the end of the experiment when they were killed in good health.

The heart weight has been expressed as a cardiac index (the ratio of heart weight to body weight x 10^{-4}), and it will be seen that there is a significant difference between the two groups (table X). Low power views of sections through the hearts of the triiodo-thyronine pair and one of the thyroid pair are shown in fig. 66 alongside a control rat heart, and the remarkable degree of hypertrophy will be apparent. The four individual sections are shown in figs. 67, 68, 69 and 70.

The heart of the one of the pair of thyroid animals was weighed not only in the fresh state but also after drying. Similarly the dry weights of the hearts R75 and R78 (two of the control animals) were estimated.

The increase in weight seen in the heart of the thyroid treated rat was not due to oedema but to the increase in amount of tissue of which the heart was formed.

Histology of the two remaining control hearts revealed no abnormality but in the hearts from the animals treated with these high doses of triiodo-thyronine and thyroid, hypertrophic fibres were in places infiltrated by plasma cells, and occasional large mononuclear histiocytes. No areas of frank necrosis were seen although there was one focus of fibrosis in which cellular activity was quite marked suggesting repair.

following necrosis.

Conclusion

Thyroid (B.P.) and triiodo-thyronine given in doses of gr. i and 20 µg. respectively for eight weeks, produces an increase in heart weight which does not appear to be related to the increase in water content. The histological appearances are consistent with the suggestion that myocardial hypertrophy is the cause of this increase in weight.

Experiment G.

Varying the grade of hypoxia to which to expose the heart is probably most easily done by varying the haemoglobin level of the blood. However, it is not true to consider that by reducing the haemoglobin level of the blood the haematological factor is the only one being varied. In fact almost certainly the myocardial factor, hypertrophy, is also of importance.

Thus before proceeding with the critical experiment of varying the grade of hypoxia to attempt to produce varying grades of myocardial damage in already structurally abnormal myocardium, the effect of anaemia upon the hearts of rats was investigated.

In spite of the widespread belief that the cardiac hypertrophy does occur with anaemia, Stembridge and Rigdon (1952) have indicated the lack of evidence to support any of the reported cases. Their report of only one acceptable heart hypertrophy in autopsies of seven persons with sickle cell anaemia emphasises the paucity of authentic examples of cardiac hypertrophy due to anaemia in man. Re-investigating this problem by producing an anaemia by means of phenylhydrazine, Norman and McBroom (1958) found that an enlargement of the heart could be produced. Their results indicated that "the mechanism of hypertrophy under these conditions may be one of myocardial injury rather than mechanical."

Haemoglobin levels of the experimental group of rats were reduced by repeated venesection. Initially 1-2 ml. of blood was taken twice weekly; after three weeks 5-6 ml. of blood daily was taken from these animals in whom after the first three weeks, the increased marrow activity was indicated by a marked peripheral erythrocytic polychromatophilia.

Control animals were subjected to the same pre-injection warming, tail vein constriction, towel rolling and venepuncture as the experimental animals. Every

attempt was made to eliminate false results which might be produced by "stress" lesions of the myocardium as suggested in the voluminous literature of Selye.

The results of bi-weekly haemoglobin estimations are given in figs. 71 and 72.

The animals were kept in two groups (table XI). To test the effect of exercise on anaemic rats, four animals undergoing venepuncture (R54, R55, R56 and R57) and three control animals were kept in cages set at 45°, the food and water being at the upper end of the cage. These animals could sleep comfortably in the angle at the bottom of the cage but all feeding excursions demanded a walk up the 45° slope and some exertion was required to maintain their position at the feeding hoppers. Rats 47, 52, 53, 58 and 61 were venepunctured and kept in horizontal cages, and five more animals served as controls for this group.

None of the rats died during this experiment which lasted three months. Approximately one month was spent reducing the haemoglobin concentration from 14.5-16.0 G/100 ml. to 10.8-13.6 G/100 ml. Over the next three weeks this was further reduced to 4.96-8.6 G/100 ml. Following this, the haemoglobin level reached was maintained for four more

weeks, by approximately weekly venepuncture.

Two of the animals, R53 and R65, were found to have lung abscesses at necropsy. The other rats appeared healthy with the exception of some with cardiac hypertrophy.

Blood Haemoglobin and Cardiac Index

In six animals an anaemia in which the haemoglobin level was reduced to 7.36 G/100 ml. (50%) or less, was produced by repeated venepuncture (figs. 71 and 72). In one animal there was a haemoglobin reduction to 9.92 G./100 ml. In these seven rats the cardiac index was raised by comparison with the control group and the two animals in whom venepunctures did not result in an anaemia before venepuncture was no longer possible (table XI). From the two hearts which were dried the increase in cardiac weight was shown to be due not to an increase in water content but to an increase in the amount of tissue of which the heart is formed.

There was no significant difference in heart index between the tilted and horizontal anaemic rats and the tilted and horizontal normal rats. The tilted envir-

onment made no significant contribution to the production of hypertrophy.

Histologically in the hypertrophied group there were scattered and scanty foci of myocytolysis and fibrosis (fig. 73) in relation to which a few lymphocytes were seen. The changes seen did not differ significantly from those noted in the myocardium of the thyroid and triiodo-thyronine group of rats.

Conclusions

Cardiac enlargement, due to an increase in the amount of tissue of which the heart is formed, occurs in anaemic Hooded Lister rats. In this experiment, the anaemia was induced by repeated venepuncture. The haemoglobin level beyond which hypertrophy was seen was 7.36 G/100 ml. This and lower levels were maintained for five weeks, considerable care having been taken to cause a reduction of the haemoglobin level from normal by slow stages and to avoid producing a degree of haemorrhage causing shock.

The effect of living in a cage tilted at 45^{o} to the

horizontal did not have any significant effect on the hearts of either the anaemic or normally haemoglobinised animals.

Experiment H.

The study of the early morphological alterations of myocardial "ischaemia" have been studied extensively by means of light microscopy but so far, only a relatively few investigators have reported their findings on electron microscopy. The use of the term "ischaemia" is in this context defensible in view of the fact that coronary ligation has been the means by which a severe disproportion between the oxygen available and the oxygen required has been brought about by most investigators.

Rabbits were used by Caulfield and Klionsky (1959), and rats were used by Bryant and his colleagues (1958). Both these groups of workers ligated branches of the left coronary artery under anaesthesia and removed the heart at varying times after the open-chest, coronary-ligating operation. In Caulfield and Klionsky's paper no details are given of procedure carried out on the control animals. From the discussion it can be inferred that the control group was in fact operated upon, but the extent to which

this operation compared with the coronary ligation procedure is not given. In the series of Bryant, Thomas and O'Neal control material was taken from the posterior portion of the left ventricle. These authors also killed two of their animals immediately after the operation and kept their bodies at a temperature of 37°C. Blocks of tissue were taken hourly for five hours to determine the effects of autolysis and to compare these changes with those of infarction.

Anaesthesia, thoracotomy, positive pressure respiration, and the handling of the coronary vessels introduce possible sources of error and only by the strictest control can material derived from such experimental work be evaluated. It was in an effort to do this that the following experiment was carried out.

Six white mice were lightly anaesthetised by ether inhalation. A small incision was made in the left chest of two animals (Group A) in the mid-axillary line, care being taken to avoid haemorrhage. The left thoracic cavity was opened and kept open. The heart continued beating and although the rate rose, the animals survived the twenty-three minutes following the opening of the left chest. At this point the heart was removed from each animal. In another two mice (Group B) the left side of

the chest was opened as in Group A, and again the heart rate rose. Ten minutes later the right pleural cavity was opened into. The heart of one of the mice started beating irregularly three minutes later but continued to beat for another four minutes. The heart was removed twenty minutes after the start of the operation. The heart of the second mouse of this pair was by this time still beating irregularly and that was removed by twenty-five minutes after the production of the left pneumothorax. The last two animals (Group C) were lightly anaesthetised for twenty-five minutes following which their hearts were removed within a minute of opening their chests.

The hearts were speedily cut and treated as described on pages 35 to 39.

No facilities were available to estimate the blood oxygen levels of the four groups but the experiment was planned to produce different grades of hypoxia by unilateral and bilateral pulmonary collapse. The critical question was how long would the white mouse heart go on beating, if only irregularly, following opening both pleural cavities. Fortunately, this was found to be in the region of ten minutes.

The mechanical disadvantage of cardiac action in an animal, one side of the chest of which is open, is condid-

erable. Some attempt was made to control this disadvantage by comparison with animals in whom both pleural cavities had been opened, and with normal but anaesthetised animals.

Results

Electronmicrographs of normal mouse myocardium were obtained from the control animals of Group C. This material is illustrated in figs. 82, 83, 85 and 86, and discussed in Chapter Two.

In the animals of Group A, in which the left pleural cavities were opened, no significant abnormality was detected on electronmicroscopy. A few fields in which occasional mitochondria were suspect were photographed in this material but the results were of the type seen in fig. 74 where refocussing resolves the cristae of the mitochondria in which some damage might be suspected.

The morphological changes seen in the hearts of the mice in Group B were mainly related to the mitochondria, and to some extent the endoplasmic reticulum. The mitochondrial swelling, vacuolation and the loss of many cristae, are easily recognised in figs. 75 to 78. However, by no means are all the internal membranes ruptured or dissolved and

the limiting double mitochondrial membrane is still recognisable in even the badly damaged mitochondria. In fig. 78 the mitochondrial double membranes are seen and no nuclear abnormalities (fig. 76) were found. There was a generalised dilatation of the endoplasmic reticulum.

No evidence of myofibril or filamentous abnormality was seen.

Discussion

Within five minutes of arterial ligation Caulfield and Klionsky saw intracellular spaces between the myofilaments. However, when their illustrations are examined, the resolution of their electronmicroscopy can be seen to be far from ideal and the intracellular spaces appear to be of dubious significance. However, as in this experiment there is some measure of agreement that mitochondrial abnormalities are of early onset as is swelling of the endoplasmic reticulum. These changes are probably brought about by hyperosmolarity (Bryant et al.)

These morphological abnormalities are in no way qualitatively different from those described following autolysis. However, the autolytic process causes a consider-

ably slower development of structural change than is seen in areas of myocardium in which a reduced oxygen tension has been present.

There is one point which has so far escaped critical evaluation. The tissue response to fixation may well alter under differing degrees of anoxia and there is no certainty that the artefact so caused will in fact be constant. It is this factor and the similarities of autolytic and hypoxic morphological changes that make the assumption that a process exactly similar to the one described actually does occur in the intact animal when the critical level of hypoxia is reached in the myocardium.

Conclusion

By means of the production of a bilateral pneumothorax in the mouse, in twenty minutes severe morphological changes were produced in the mitochondria of the myocardium. These changes were accompanied by a swelling of the endoplasmic reticulum and were related not to mechanical disturbance of the heart but probably to the hypoxia resulting from an open chest.

CHAPTER ELEVEN

SUMMARY

This thesis is a study of the pathological reactions of the myocardium. Based on a survey of the normal myocardial structure as revealed by light and electron microscopes, this work has been carried out from the macroscopic and histological examination of a series of one hundred and twenty-five hearts obtained at unselected routine autopsies, material from the hearts of ten children who died from diphtheria, and the heart of one child in whom a diagnosis of idiopathic cardiomegaly was made at autopsy.

Before critical examination of the histology of this material could be carried out research into technical methods for the processing and staining of the myocardium was necessary. Using methods, many of which were discovered and developed by Lendrum and his school, the technical difficulties of preparing myocardium for histological examination have been largely overcome and a new staining sequence based on the principle of Masson has been evolved. Using phloxin and milling yellow on sections previously subjected to "degreasing", it has been possible to differentiate the red by means of the yellow dye, to demonstrate normal myofibrillar

and intercalated disc patterns, or by allowing further differentiation, to demonstrate abnormalities in the internal arrangement of the cells of the myocardium.

Physiological and pathological growth of the myocardium has been studied. By micromeasurement of normal hearts, and hearts in which right and/or left ventricular hypertrophy has taken place, an attempt has been made to assess the validity of Linzbach's theory of cardiac enlargement. The results of fibre thickness measurements in relation to individual ventricular weights have been tested by a statistical analysis of their relation to age and sex, and a series of clinical subgroups. The significance of these figures is acceptable. Fibre thicknesses have been plotted against ventricular weights on logarithmic graphs and the summarised median values (figs. 96 and 97) show that right ventricular fibre size increases as the cube of the weight up to about eighty per cent above the normal figure for the right ventricle. In the left ventricle fibre size increases as the square of the weight to about thirty per cent above normal for the left ventricular weight. Above these weights, there is a tendency for the fibre size to fall suggesting that an increase in the number of fibres occurs. However, the statistical significance of these graphs beyond

the stage at which the fibre size falls has not been established owing to the small number of observations in the upper range of heart weights.

The morphological changes in hypertrophic muscle are described, "hypertrophy" being defined by an increase in the weight of the ventricles after dissection and separation. The causes of left ventricular hypertrophy and right ventricular hypertrophy found in the hearts of the routine autopsy series are discussed. In fifty per cent of the examples of the "L.V. hypertrophy" group (of forty-two cases) hypertension was considered to be the cause of the increased ventricular weight. The role of coronary atheroma in the production of myocardial hypertrophy is discussed and in the "L.V. hypertrophy" group twenty patients (nearly half) were found to have gross coronary disease and of these, in six cases the disease of the coronary arteries was the only reason found to account for the cardiomegaly.

From the study of this series cardiac hypertrophy has been found to be a likely if not invariable result of chronic anaemia.

Six examples of left ventricular hypertrophy were due to disease of the aortic valve. Only in one case was it possible to prove that chronic pulmonary disease with right

ventricular hypertrophy was responsible for the production of left ventricular enlargement.

In a discussion of the causes of right ventricular hypertrophy, a plea is made for the abandonment of the term "cor pulmonale" on the grounds that this term is interpreted in different ways by different groups of workers. "Cardiopulmonary disease" is a preferable phrase which does not purport to mean more than it says. In eleven of the "R.V. hypertrophy" group (of which there were thirty-two examples) chronic pulmonary disease was present. In the three cases of mitral stenosis right ventricular hypertrophy was also present. It is often said that a common cause for right ventricular hypertrophy is failure of the left heart. Although this has by no means been borne out by this study, it is considered that as the tension generated by the right ventricle provides mechanical support for the ventricular septum, contributing to the strength of this wall and to the left ventricle as a whole, left ventricular hypertrophy may induce a compensatory hypertrophy in the right heart. Another possibility is that the bundle arrangement of the myocardium is such that the stimulus and metabolites leading to hypertrophy in the left ventricle will extend some way into the right myocardium.

A case of idiopathic cardiomegaly has been studied and the causal hypotheses have been discussed. Functional and development theories are being given greater credence in view of the number of reports of cases of functional outflow tract stenosis. An abnormality of timing of the individual muscle bundles and an abnormality of the orientation of constituent parts of the superficial sino-spiral and bulbospiral bundles are suggested as possible causes of hypertrophy worth further investigation.

The grade of hypoxic injury inflicted on the myocardium is determined by the degree of disproportion between the oxygen required by, and the oxygen available to, the heart muscle. Hypoxia in absolute terms is dependent on the mechanical factors reducing the lines of supply of blood to the heart (the coronary factors), and the physical factors affecting the oxygen carrying power of the blood (the haematological factors). The effect of this absolute hypoxia is determined by its relation to the myocardial mass, its metabolic state and the efficiency of the heart to use what oxygen is available. These have been called myocardial factors. The frequency with which these factors have been encountered in sixty-two patients of the routine autopsy series who were found to have hearts in which the changes of relative myocardial hy-

poxia has been demonstrated, has been assessed. In the fifteen cases in which extensive acute infarction of the heart was found, coronary atheroma was severe and in eleven of these, occlusions were demonstrated in the vessels. However, when considered as a group, of all the cases of acute myocardial infarction (varying from large to microscopically small) fifty-five per cent had gross coronary disease, nineteen per cent had moderate atheroma and in twenty-six per cent minimally atheromatous or normal coronary arteries were found. Undoubtedly the large number of cases of infarction without significantly involved coronary vascular disease was related to the fact that many blocks of each heart were examined and the number of microinfarctions found was relatively large. Of three cases of bacterial endocarditis evidence of coronary embolism was found in two. The role of coronary angio-spasm is discussed. One case of giant cell coronary arteritis is reported.

In thirty of the forty-two cases of the "L.V. hypertrophy" group infarctions, acute, healing and healed, were found. Of the thirty-two cases of the "R.V. hypertrophy" group, infarction involved the right ventricle (often secondarily from the left side) in eleven cases. Undoubtedly in many cases hypertension and the coronary artery and

arteriolar disease with which it is associated, is the link between hypertrophy and the frequency with which infaretion occurs in the myocardium. However, there are other cases in which hypertensicn cannot be incriminated and in these the explanation usually suggested is that "the myocardium grows away from its blood supply". This is only part of the answer. "Functional myocardial stress" is considered to play a significant role in the susceptibility of an increased myocardial mass to hypoxia.

The importance of fibrosis of the myocardium and myocarditis in weighing down the myocardial factors in a consideration of relative myocardial hypoxia are discussed. Whether by local mechanical effects or by the associated increase in the metabolic demands made by the inflamed myocardium, myocarditis may play a part in the production of relative myocardial hypoxia as in half of the cases of myocarditis seen in this autopsy series changes of relative myocardial hypoxia have also been seen. Shock, anaemia, hypoxaemia and blood viscosity are discussed as "haematological factors" of hypoxia.

Although the mechanical coronary factors are of the utmost importance in the production of relative myocardial hypoxia, if all infarcts, large and small, are considered

together, a surprisingly high percentage (in this series about twenty per cent) are associated with haematological and myocardial factors entirely. It is for this reason that attempts should be made to avoid the use of the terms "coronary heart disease", "coronary insufficiency" and so on. In many cases the incrimination of the coronary vasculature is correct but in many cases it is not. This nomenclature is one of inaccuracy and despair for, at present, there is nothing the physician can do about the established coronary factors. The term relative myocardial hypoxia demands a consideration not only of coronary factors but of haematological and myocardial factors for which there is much that can be done medically and occasionally surgically to reduce these factorial values.

A series of graded hypoxic injuries to the myocardium has been studied. A somewhat restricted definition of acute infarction has been used; if as a result of interaction of coronary, haematological and myocardial factors, a local hypoxia results in a coagulation necrosis of sufficient severity to elicit a neutrophil polymorph response, that area in which necrosis has occurred is said to be acutely infarcted. Using this morphological pattern as a base line,

"glycogenic" degeneration, focal myocytolysis, and fatty change have been found to have a high correlation with manifestly hypoxic lesions and are considered to be authentic, but not specific, patterns of varying intensities of hypoxia. Finally the term acute hypoxic myocardial degeneration is introduced to describe the morphological changes occurring in muscle as it dies. This change has been inaccurately described as "early infarction". However, the "acuteness" of the hypoxic process and basically, its extent, will determine whether or not a polymorph leucocytic infiltration will occur. If it does, stromal damage probably already inflicted to some extent by the original hypoxic insult, is contributed to by heterolysins from the leucocytes. Ingress of macrophages is facilitated and healing is brought about by scarring. It is suggested from this study that the classical descriptions of the healing of an infarct by the proliferation of fibroblasts and the ingrowth of newly formed capillaries is seen only when haemorrhage and fibrin deposition occur within the myocardium. The usual mode of healing is brought about after polymorph leucocytic infiltration of the area by the concertina-ing of reticulin and its condensation to form a temporary fibrous tissue repair. There follows a recolonisation of pre-existing capillary channels by the ingrowth

of endothelium. The remarkable vascularity of the absorption zone maintains macrophage activity and results in the stimulation and mitosis of resting mesenchyme tissue cells, which by fibrogenesis "weave the weft" into the collapsed reticulin "warp".

Alternatively if the conditions responsible for acute hypoxic degeneration are such that no polymorph leucocytic exudation is brought about, myocytolysis will ensue, a process largely dependent for its resolution on autolysins and local macrophage response. The importance of the differentiation between myocytolysis and infarction is pathologically important in view of the likelihood of reversibility of the cytolytic lesions. This theory has been evolved following a comparative study of acute diphtheritic myocardial degeneration and the myocarditides. Toxic damage to the myocardium results in a parenchymatous degeneration in myocardial cells followed by interstitial cellular reaction. The degenerative changes are usually unaccompanied by significant stromal damage and it is suggested that replacement of myocardium results from adjacent cell hypertrophy.

In the routine autopsy series in fifteen cases evidence of past or present myocardial inflammation was seen. These

examples of myocarditis are discussed under four headings, rheumatic, organismal, chemical and toxic and "isolated" myocarditis. The criteria for the diagnosis of myocarditis must be strictly applied if the diagnosis is to merit clinical association. From the results of this survey, although it is possible to agree with Saphir, de la Chapelle and others that the incidence of myocarditis (excluding rheumatism and diphtheria) is in the region of ten per cent, only in two patients did it significantly directly contribute to the cause of death. However, it is possible that myocarditis could considerably weigh down the myocardial factors to increase the susceptibility of these hearts to hypoxic change.

The reported incidence of myocardial metastatic involvement in cases of malignant disease varies from as low as two per cent to as high as twenty-one per cent. Much of the difference in incidence is related to the extent to which the heart is examined. In twenty-four cases of the routine autopsy series, carcinoma was diagnosed and in four of these patients, secondary myocardial deposits were found. In only five of the twenty-four cases did a cancer fail to metastasise to the heart having escaped the confines of the local tissues and lymph nodes. In other words, in this

series, if the primary tumour had the invasive properties to spread through the local and regional lymph node barriers, the growth had not far short of a fifty-fifty chance of metastasising to the heart.

In six cases a diagnosis of malignant lymphoma was made. In all these cases extensive myocardial changes were seen, the myocardium in one patient with lymphosarcoma and two with leukaemia being infiltrated by primitive cells. However, the outstanding myocardial damage noted in all six patients was hypoxic in origin, largely contributed to by the anaemia associated with the malignant lymphoma group of diseases.

Two cases of cardiac amyloidosis and one of auricular myocardial proteinosis were found on microscopy of the routine autopsy series. The amyloid cases were examples of a group in which amyloidosis is localised principally in the heart and it is suggested that the disease results in aged people from a defect in protein synthesis and absorption, a relative hyperglobulinaemia leading to a leakage of globulin into the tissues and the deposition of amyloid substance. Why the myocardium should be picked out preferentially by this process is not understood.

Relative myocardial hypoxia is without doubt the gravest

and most common problem in myocardial pathology. In a consideration of its causation, absolute measurement of the coronary factors can be made at autopsy and that of the haematological factors can be made in life. However, in view of the difficulty of assessing the role of the myocardial factors a series of pilot experiments were carried out to answer this question. Experimental attempts to produce a graded myocarditis in rats by toxins failed. By administration of chlorothiazide and desoxycorticosterone acetate implants or cortisone acetate injections, hypokalaemic necrosis followed by healing was produced. A continuing myocardial inflammation was not achieved. On the other hand, hypertrophy without coronary vascular disease was produced in rats by thyroid or thyroxine administration, by replacing tap drinking water with 1% saline, and by anaemia caused by repeated venesection. The susceptibility of abnormal myocardium to oxygen lack can be tested by subjecting these animals to a brief phase of severe hypoxia for a short time and examining the myocardium under the electron microscope. The normal hearts of mice were subjected to such an episode and the early degenerative changes seen on electronmicroscopy are described, consideration being given to the complications of autolytic processes with which early hypoxic change may be confused.

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T A B L E S

1 to X111

TABLE I.

Case No.	Sex	Age	B.P. mm.Hg.	L.V. weight (G)	L.V. fibre size (units)	R.V. weight (G)	R.V. fibre size (units)	L.V./R.V. ratio	Cause of hypertrophy.	Clinical details and autopsy diagnosis.	Cor. Ath.	Left ventricular Fib.	Ac.Inf.	Ac.Degn.	"Glycog." degn. and/or myocytolysis.
3381	M	55	106/80	315	81	140	75	2.3	R.V. hypertrophy.	Bronchopneumonia. Emphysema. Pulm.emb.	+	++	-	-	+
3386	M	78	146/90	250	91	88	76	2.8	Hypertension	Bronchopneumonia	++	++	-	-	+
3387	F	73	110/75	245	90	95	76	2.6	Aortic stenosis	Aortic and mitral stenosis.	-	+	-	-	-
3389	M	52	138/80	195	75	70	70	2.8		Influenzal bronchopneumonia.	+	+	-	-	-
3392	M	39	100/70	272	110	128	80	2.1	Aortic stenosis	Aortic and mitral stenosis. Bronchopneumonia.	+	++	-	+	-
3394	M	73	Shock	200	85	70	65	2.9	Hypertension	Pulm. embolism. Unresolved pneumonia	+	+	-	-	-
3396	M	80	146/100	245	75	104	80	2.4	Hypertension Hb.10.5 G%	Bronchopneumonia Emphysema.	+	+	-	-	-
3397	M	63	112/84	390	78	95	44	4.1	Aortic stenosis	Influenzal bronchopneumonia. Myocardial infarction.	+++	+++	++	+++	++
3400	F	65	130/75	277	93	85	65	3.3	Hypertension Hb. 9.6 G%	Diabetes. K.W. nephropathy. Uraemia. Myocardial infarction.	+++	+++	++	++	+++
3403	F	73	100/80	240	80	80	68	3.0	Hypertension	Perf. duod. ulcer. Peritonitis. Myocardial infarction.	+++	+++	+	++	-
3408	F	58	225/120	214	86	50	56	4.3	Hypertension	Cereb. thrombosis	+++	+++	-	+	++

TABLE 1 cont.

3409	M	84	Shock	280	100	80	63	3.5	Hypertension	Cholangio-hepatitis Bronchopneumonia. Myocardial infarction.	+	++	+	++	+
3417	M	88	110/70	280	100	70	65	4.0	Hb. 11.2G%	Hypothermia. Peripheral gangrene.	+	++	-	+	+
3418	M	53	"normal"	215	95	85	70	2.5		Post-operative collapse. Fibrinous pleurisy and left sub-phrenic abscess.	+	++	-	-	-
3420	F	75	224/124	260	110	57	56	4.6	Hypertension	Bronchopneumonia. Left hemiplegia.	++	++	-	+	-
3422	M	81	120/70	217	97	68	70	3.2	Hb. 6.08G%	Organising lobar pneumonia. Bacterial endocarditis.	-	+	+	++	++
3429	M	59	140/90	240	75	52	54	4.6	Hypertension Hb. 8.4G%	Rheumat. arthritis. Bronchopneumonia. Myocardial infarct.	+++	+	+++	+++	+++
3436	M	59	180/100 98/70	225	102	74	65	3.0	Hypertension	Coronary thrombosis. Myocardial infarct.	+++	++	-	++	+
3443	M	76	150/85	208	95	61	70	3.4	Hypertension	Pneumonia with abscess formation.	-	-	-	-	-
3448	F	83	230/130	210	93	48	55	4.4	Hypertension	Myocardial infarct.	+++	+++	++	++	-
3456	M	64	Shock	202	72	55	61	3.7	Cor. atheroma	Retrosternal pain (death 3 hrs. later)	+++	+	-	+	+
3458	F	72		196	72	43	50	4.6	Cor. atheroma	Bronchopneumonia. Gastric carcinoma.	+++	+++	-	-	-
3463	M	78	120/70	290	95	60	70	4.8	Hb. 4.3G%	Acute cystitis	-	++	-	++	+
3468	M	46	90/? 140/110	220	80	56	60	3.9	Hypertension	Subarach. hage.	-	-	-	-	-

TABLE I cont.

3470	F	75		274	89	61	69	4.5	Aortic stenosis	Myocardial infarct.	+++	+++	++	+++	+++
3473	F	72	105/70	211	82	43	55	4.9	Cor. atheroma Hb.10.0G%	Myocardial infarct.	+++	++	++	++	++
3476	M	90	174/100	314	89	105	86	3.4	Hypertension	Emphysema. Myoc. infarction.	+++	+++	++	++	+
3487	M	42	150/94	197	89	133	85	1.3	Hypertension	Sub-acute nephritis	-	+	-	+	+
3491	M	78		215	94	54	58	4.0	Cor. atheroma	Gastroenterostomy	+++	+++	-	-	-
3495	M	57	110/80	203	90	58	62	3.5	Cor. atheroma	Myocardial infarct.	+++	+++	++	++	+
3496	M	62	140/90	243	85	58	67	4.2	Hypertension	Ulcerative colitis. Bronchopneumonia.	++	+++	-	++	++
3503	M	67		201	86	45	62	4.5		Ca. pancreas. Biliary cirrhosis.	+	+	-	-	-
3512	M	57		280	102	55	68	5.1	Hypertension	Myocardial infarct.	+++	+++	++	++	++
3538	M	65		256	94	97	79	2.6		Gastric carcinoma. Pulm. embolism.	-	++	-	-	-
3541	M	67	142/74	230	80	85	76	2.7		Bronchopneumonia	-	+	-	-	-
3565	M	64	135/75	375	90	86	68	4.3	Cor.thrombosis Hypertension	Cor. thrombosis	+++	+++	-	-	++
3607	F	60	160/110	190	86	70	63	2.7	Hypertension Hb. 11.2G%	Cor. thrombosis	+++	+++	-	++	++
3610	F	79	160/100	228	86	58	61	3.9	Hypertension	Giant cell arteritis	+++	+	++	++	+
3626	M	38	110/80	263	98	104	79	2.5	Cor. atheroma	Cor. thrombosis	+++	+++	-	-	++
3689	F	74	110/65	254	86	55	60	4.6	Aortic stenosis Hb. 8.16 G%	Myocardial infarct.	+	+++	+	+	-
3737	M	70	90/60	193	78	75	73	2.6	Hypertension	Organising pneumonia	+++	++	++	+	-
3773	F	33	120/78	198	82	110	86	1.8	Aortic stenosis	Aortic, mitral and tricuspid stenosis. Pulm. art. thrombosis	-	+	-	-	++

TABLE II.

Case No.	Sex	Age	B.P. mm.Hg.	L.V. weight (G)	L.V. fibre size (units)	R.V. weight (G)	R.V. fibre size (units)	L.V./R.V. ratio	Cause of hypertrophy.	Clinical details and autopsy diagnosis.	Cor. Ath.	Right ventricular Fib.	Ac.Inf.	Ac.Degn.	"Glycog."degn. and/or myocytolysis.
3381	M	55	106/80	315	81	140	75	2.2	Emphysema	Bronchopneumonia. Cereb. softening.	+	+	-	+	+
3386	M	78	146/90	250	91	88	76	2.8	L.V. hypert. (Hypertension)	Bronchopneumonia	++	-	-	-	-
3387	F	73	110/75	245	90	95	76	2.6	Mitral stenosis	Aortic and mitral stenosis. Mult. pulm. emb.	-	++	-	++	++
3388	M	68	160/80	155	83	105	98	1.5	Emphysema	Bronchopneumonia	++	+	+	++	-
3389	M	52	138/80	195	75	70	70	2.8		Bronchopneumonia	+	+	-	-	-
3392	M	39	100/70	272	110	128	80	2.1	Mitral stenosis	Aortic and mitral stenosis	+	-	-	-	+
3394	M	73	Shock	200	85	70	65	2.9	L.V. hypert. (Hypertension)	Unresolved pneumonia Pulm. embolism	+	+	-	++	-
3395	F	61	100/65	166	74	110	90	1.5	Emphysema	Bronchopneumonia	+	-	-	-	-
3396	M	80	146/100	245	75	104	80	2.4	Emphysema	Bronchopneumonia	+	-	-	-	-
3397	M	63	112/84	390	78	95	44	4.1	L.V. hypert. (Aortic stenosis)	Bronchopneumonia Myocardial infarct.	+++	++	++	+++	-
3399	M	52		128	60	120	80	1.1	Emphysema	Bronchopneumonia	-	++	++	++	++
3400	F	65	130/75	277	93	85	65	3.3	L.V. hypert. (Hypertension Hb. 9.6 G%)	Diabetes. K.W. nephropathy. Bronchopneumonia.	+++	+	-	++	-
3402	F	76		155	79	100	65	1.5	Emphysema	Bronchopneumonia	++	+	++	+	-
3403	F	73	180/100	240	80	80	68	3.0	L.V. hypert. (Hypertension)	Perf. duod. ulcer Peritonitis.	+++	+	-	-	-
3404	F	58	138/80	154	76	98	62	1.6	Emphysema	Bronchopneumonia	-	-	-	-	-

TABLE II cont.

3409	M	84	Shock	280	100	80	63	3.5	L.V. hypert. (Hypertension)	Cholangiohepatitis Bronchopneumonia	+	-	-	-	-
3417	M	88	110/70	280	100	70	65	4.0	L.V. hypert. (Hb. 11.2 G%)	Hypothermia Peripheral gangrene	+	+	-	++	-
3418	M	53	"normal"	215	95	85	70	2.5		Post-oper. collapse Fibrinous pleurisy L. sub-phren.abscess	+	-	-	-	-
3421	M	57	100/70	165	80	115	86	1.4	Lobectomy Pulm. fibrosis	Ca. bronchus Bronchopneumonia	-	+	-	++	-
3432	M	72	140/90	160	75	73	56	2.2	Emphysema	R. pneumothorax	++	-	-	-	-
3436	M	59	180/100 90/70	225	102	74	65	3.0	L.V. hypert. (Hypertension)	Coronary thrombosis. Myocardial infarction.	+++	-	-	+	+
3444	M	57	130/90	186	80	95	75	1.9	Emphysema	Bronchopneumonia	-	+	-	++	-
3476	M	90	174/100	314	89	105	86	3.0	Emphysema	Bronchiectasis Cor. thrombosis	+++	++	++	++	+
3487	M	42	150/94	177	89	133	85	1.3	Pulm. emboli	Sub-acute nephritis	-	+	-	++	+
3538	M	65		256	94	97	79	2.6	Pulm. embolism	Ca. stomach	-	++	-	-	-
3541	M	67	142/74	230	80	85	76	2.7		Bronchopneumonia	-	-	-	++	-
3565	M	74	135/75	375	90	86	68	4.4	L.V. hypert. (Hypertension)	Cor. thrombosis	+++	+	-	+	+
3607	F	60	160/110	190	86	70	63	2.7	"	Cor. thrombosis	+++	+	-	-	+
3626	M	38	110/80	263	98	104	79	2.5	L.V. hypert. (Cor. atheroma)	Cor. thrombosis Pulm. infarcts.	+++	+	-	-	+
3737	M	41	90/60	193	78	75	73	2.6	L.V. hypert. (Hypertension)	Organising pneumonia	+++	-	-	-	-
3752	M	76	150/95	138	78	135	83	1.0	Cardiac amyloid	Cardiac amyloid	++	+	++	++	++
3773	F	33	120/78	198	82	110	86	1.8	Mitral stenosis	Aortic, mitral and tricuspid stenosis. Pulm. art. thromb.	-	+	-	-	-

TABLE III

Case No.	Sex	Age	Hb. level (G% or Sahli)	Left Ventricle Weight (G)	Left Ventricle Fibre size (units)	Right ventricle Weight (G)	Right ventricle Fibre size (units)	Clinical details and diagnosis
3385	M	22	-	165	84	65	70	Vesico-ileal transplant. Peritonitis.
3398	M	74	110	127	70	53	54	Bilat. mid-thigh amput. Broncho-pneumonia.
3412	M	46	-	157	70	49	56	Cirrhosis of liver.
3414	M	36	-	140	68	50	53	Ulcerative colitis. Post-op. collapse (ileostomy)
3415	F	51	59	94	55	34	53	Ulcerative colitis. Colectomy. Subphren. abscess. Broncho-pneumonia.
3416	F	63	-	96	60	42	42	L.int. carotid artery thrombosis. Broncho-pneumonia.
3424*	M	60	-	130	72	60	70	Small int. obstruction.
3423	F	65	-	158	79	60	55	Uraemia. Chronic cholangitis.
3426	F	69	9.9	135	70	30	51	Gastric carcinoma with perit. seconds. Cirrhosis of liver.
3428	M	58	-	166	75	46	56	Multiple injuries.
3431	F	69	-	124	67	35	45	Cerebral haemorrhage.
3437	M	73		115	68	32	55	Bronchiectasis and abscess formation. Failure of resolution (lobar pn.)

TABLE III cont.

3439	F	65	11.34	135	70	40	44	Ruptured cereb. aneurysm. Broncho-pneumonia.
3440	F	69	-	132	60	40	42	Int. carotid art. thrombosis. Cereb. infarct.
3442	F	71	9.8	130	69	36	65	Cereb. haemorrhage.
3446	F	75	8.9	93	60	20	50	Hiatus hernia. Pulm. embolism
3447	M	61	-	125	72	47	50	Carcinoma of pancreas. Mult. metastases. Pulm. infarction.
3459	M	53	-	140	70	45	55	Laparotomy. Gastric carcinoma. Broncho-pneumonia.
3460*	F	67	-	155	57	36	56	Rupture of bladder. carcinoma of bladder.
3461	F	81	9.8	138	60	50	55	R. empyema. Pneumonitis. Bronchi-bronchio-lectasis.
3471	F	57	-	95	62	30	54	Carcinoma colon. Seconds in liver, lymph nodes and ovary.
3478	F	75	12.3	90	62	25	50	Gastric carcinoma. Seconds in liver and lymph nodes.
3482	M	88	12.6	154	74	60	68	Carotid artery thrombosis. Broncho-pneumonia.

TABLE III cont.

3483	M	42	-	166	78	45	58	Choledochoduodenostomy. Post-op. haemorrh.
3485	F	49	40	137	68	30	49	Carcinoma cervix uteri. Pyelonephritis. Broncho-pneumonia.
3486	M	50	-	115	66	27	48	Uraemia after nephrolithotomy.
3492	M	72	12.3	146	76	38	56	Subacute pyelonephritis. Broncho-pneumonia.
3498*	M	66	-	180	82	53	68	Haemorrhage from aneurysm of aorta.
3507*	M	82	-	145	65	50	49	Intestinal obstruction. Laparotomy. Broncho-pneumonia.
3516	F	58	-	108	60	38	48	Pulm. embolism (post-oper.)
3518	M	67	-	137	68	54	55	Adrenal carcinoma. Seconds. in lymph nodes and liver.
3519*	M	66	-	160	78	43	53	Carcinoma colon. Laparotomy. Perf. of bowel.
3521	F	57	-	150	75	30	48	Cereb. haemorrh. Broncho-pneumonia.
3525	M	77	-	175	79	65	56	Empyema of gall-bladder. Liver abscess. Acute peritonitis.
3534	F	60	4.8	170	78	54	50	Glomerulonephritis.
3536	M	63	-	133	58	53	51	Perf. duo. ulcer (closed). Gastro-enterostomy. Broncho-pneumonia.

TABLE III cont.

3540	F	59	-	159	62	61	56	Fractured femur. Acute gastric dilatation.
3614	M	63	-	154	79	36	54	Pulm. embolism and pneumothorax following resection carcinoma oesophagus.
3627	F	75	-	108	58	30	42	Carcinoma uterus. Peritoneal metast-ases.
3680	M	61	-	181	81	39	50	Seminoma testis. Broncho-pneumonia.
3684	F	49	-	85	55	38	52	Acute encephalitis.
3690	M	72	-	136	58	50	48	Perf. duodenal ulcer (closed). Broncho-pneumonia.
3710*	F	70	-	188	90	63	62	Carcinoma colon. Peritonitis. Chronic bronchitis. Broncho-pneumonia.
3755	F	33	-	106	60	32	42	Bulbar encephalitis.
3781	M	63	-	152	66	58	57	Carcinoma rectum. Paralytic ileus following resection.

* = moderate coronary atheroma.

TABLE IV

Analysis of Variance

(Values in logarithms)

		Males		Females
Between sexes	(1)	.2330	(39)	
	(54)	.9455	(39)	.8213
Between age groups	(5)	.0762	(5)	.0962
Between disease groups	(6)	.2902		.3328
Residue	(41)	.5791		.3923

Summary	L.V. Weight		Disease groups.	Residue
F (39)	.8213	(6)	.3328	.4885
M (54)	.9455	(6)	.2902	.6553
F v M (1)	.2330			
(94)	= 1.9998	(12)	.6230 (80)	1.0438

msq. = .0132

s.e. = .115

By application of the Variance Ratio Test to estimate probability

$$\frac{(14)}{(80)} = \frac{.0445}{.0132}$$

$$= 3.38$$

$$\therefore p < .001$$

TABLE IV cont.

Mean values in logarithm		Left Ventricle		Right Ventricle	
		Weight	Fibre size	Weight	Fibre size
	Female	2.29_{-2}	1.91	1.81	1.81
	Male	2.19_{+4}	1.86	1.69	1.75
	s.d.	.131	.066	.188	.077
ANOVA	s.e. =	.115			

Clinical sub-groups		No.	(Derivation for overall mean for each sex)		
Hypertension	Males	6	.05	.07	.04
	Females	9	.07	.00	.03
		15	.06	.03	.00
			+.04*		
Mitral stenosis	Females	1	.20	.29	.13
Aortic stenosis	Females	2	.23	.07	.06
Mitral and	Males	3	.15	.30	.09
Aortic stenosis	Females	5	.19	.20	.11
		8	+.175*	+.24*	+.10*
			+.10*		
Emphysema	Males	7	.02	.01	-.04
	Females	3	-.11	-.05	-.06
		10	-.02	-.01*	-.05*
			-.02		
Carcinoma	Males	8	-.07	-.05	-.02
	Females	6	-.11	-.17	-.04
		14	-.09*	-.10	-.03
			-.02		
Sepsis	Males	6	-.08	-.15	-.06
	Females	3	-.03	-.11	-.02
		9	-.06	-.14*	-.05*
			-.03		
Amyloid and fatty infiltration		4	-.13	-.07	-.07
			-.05		

dW = 2dFs dW = 3dFs

* = significant results.

TABLE V.

Case No.	Sex	Age	Myocardial Factors	Haematological Factors	Coronary Factors Ath.	Coronary Factors Thr.	Clinical details and autopsy diagnosis	Myocardial: Fibrosis L.V.	Fibrosis R.V.	Myocytol. L.V.	Myocytol. R.V.	"Glycog."degn. L.V.	"Glycog."degn. R.V.	Ac. infarct. L.V.	Ac. infarct. R.V.	Ac. degn. L.V.	Ac. degn. R.V.
3381	M	55	L.V.hypert. R.V.hypert.	Emphysema Hb.12.6G% Pulm.emb.	+	-	Dyspnoeic, in C.C.F. B.P. 106/80mm.Hg. Cerebral softenings. Pulm.embolism	++	+	-	+	+	-	-	-	-	+
3386	M	78	L.V.hypert. R.V.hypert. Aur.fib.	Bronchopneu-monia. Hb.13G%	++	-	Dyspnoeic, cyanosed and in C.C.F. B.P.146/90mmHg. Death few hrs. after admission. Bronchopneumonia.	++	-	-	-	+	-	-	-	-	-
3387	F	73	L.V.hypert. R.V.hypert. R.bundle br. block.	Aortic sten-osis. Hb.13G% Pulm. emb.	-	- Aortic stenosis	In C.C.F. with 7-yr. history of prog. dyspnoea. Mitral and aortic stenosis	+	++	-	++	-	-	-	-	-	++
3388	M	68	R.V.hypert. Aur. fib.	Haem. bron-chopneumonia. Hb.11.3G% Emphysema.	++	-	Cough and breathlessness 3 months - worse in last week; in failure. Influenzal bronchopneumonia.	-	+	-	-	-	-	-	+	-	++
3392	M	39	L.V.hypert. R.V.hypert. Aur. fib.	Bronchopneu-monia. Hb.14G%	+	- Aortic stenosis	In C.C.F. with dyspnoea and haemoptysis. Haemorrhagic bronchopneumonia. Noradrenaline given.	++	+	-	+	-	-	-	-	+	-
3393	F	75		Bronchopneu-monia.Hb. 10.5G%	-	-	L. hemiplegia 12 days before death. Thrombo-atheroma of right anterior cerebral artery. E.C.G. hypertrophy with relative ischaemic pattern	+	+	-	-	-	-	-	+	-	+
3394	M	73	L.V.hypert. R.V.hypert.	Unresolved pneumonia. Shock. Pulm.emb.	+	-	Collapsed in convalescence. Unresolved pneumonia. Massive pulm. embolism (4 hrs.)	+	+	-	-	-	-	-	-	-	++

TABLE V cont.

3397	M	63	L.V.hypert. R.V.hypert.	Haemorrhagic bronchopneumonia.	+++	- Aortic stenosis	Influenza 9 days; 5 days chest pain. Myocardial infarction.	+++	++	-	-	++	-	++	++	+++	+++
3399	M	52	R.V.hypert.	Emphysema. Influenzal bronchopneumonia.Shock.	-	-	Admitted moribund having been cyanosed, dyspnoeic and oedematous 2 days. Influenzal bronchopneumonia	+	++	-	-	-	++	-	++	++	++
3400	F	65	L.V.hypert. R.V.hypert.	Bronchopneumonia. Hb. 9.6G%	+++	-	Diabetic in C.C.F. Kimmelsteil-Wilson nephropathy. Myocardial infarction.	+++	+	+++	-	+++	-	++	-	++	++
3402	F	76	R.V.hypert.	Bronchopneumonia.	++	-	Died on admission. Own doctor diagnosed pneumonia. Myocardial infarction.	++	+	-	-	-	-	-	++	-	+
3403	F	73	L.V.hypert. R.V.hypert. Myocarditis	High haematocrit. Hb.97%	+++	-	Acute abdominal pain 18 hrs. Angina for 1 year. Perf. duodenal ulcer. Peritonitis.	+++	+	-	-	-	-	+	-	++	-
3405	M	36	Noradrenaline.	Organising pneumonia.	Coronary embolism		Poliomyelitis, tracheostomy, pneumonia. Bacterial endocarditis. Myocardial infarction.	-	-	+	+	+	+	++	-	+	+
3406	F	64		Pneumonia Hb. 3.8G%	-	-	Septic arthritis, suppurative otitis media. Aleukaemic leukaemia.	-	-	-	-	+	-	+	-	+	-
3408	F	58	L.V.hypert.	Emphysema	+++	-	Angina and dyspnoea on exertion 7 years. R.cerebral thrombosis. Emphysema.	+++	-	++	-	+	-	-	-	+	-
3409	M	84	L.V.hypert. R.V.hypert.	Bronchopneumonia. Shock	+	-	Epigastric pain, vomiting, 3 hrs. followed by coma gradually deepening. Death 36 hrs. later. Cholangiohepatitis. Bronchopneumonia	++	-	+	-	-	-	+	-	++	-

TABLE V cont.

3411	F	62		Influenzal pneumonia.	-	-	Influenza for 10 days. Breathlessness and cyanosis on exertion. Collapse 8 hrs. before death. Bronchopneumonia.	-	-	-	-	-	-	-	-	-	+
3417	M	88	L.V.hypert. R.V.hypert.	Hb.11.2G%	+	-	Low output failure gangrene Hypothermia.	++	+	+	-	-	-	-	-	+	++
3420	F	75	L.V.hypert.	Bronchopneumonia.	++	-	Severe carotid and cerebral atheroma. B.P.224/124mmHg. Bronchopneumonia.	++	-	-	-	-	-	-	-	+	-
3421	M	57	R.V.hypert.	Bronchiectasis. Pulm. fibrosis. Bronchopneumonia.	-	-	Pneumonectomy for Ca.bronchus 1956. Intrathoracic metastases. Bronchopneumonia and abscess formation.	-	+	-	-	-	-	-	-	-	++
3422	M	81	L.V.hypert.	Unresolved pneumonia. Hb.6.08G%	Coronary embolism		Influenza 2 weeks ago. Admitted anuric, anaemic, dyspnoeic with tightness of chest. Organising lobar pneumonia. Bacterial endocarditis.	+	+	+	++	+	-	+	-	++	+
3427	F	85		Hb.10.5G%	+	-	Gradual mental deterioration 3 yrs. Semi-coma 3 days. Haemorrhage into a glioma.	+	-	++	-	-	-	-	-	-	-
3429	M	59	L.V.hypert.	Bronchopneumonia. Hb.8.4G%	+++	+	Rheumatoid arthritis 14 yrs. Epigastric pain 7 days. Myocardial infarction. Bacterial endocarditis.	+	++	+++	++	++	++	+++	++	+++	+
3430	M	68	L.bundle br.block	Hb.6.2G%	+++	+	Severe retrosternal pain 6 days before death. Pernicious anaemia. Myocardial infarction.	++	-	++	-	-	-	++	-	++	+

TABLE V cont.

3436	M	59	L.V.hypert. R.V.hypert.	Shock	+++	+	Productive cough 3 weeks. Paroxysmal nocturnal dyspnoea. Ankle swelling. Acute breathlessness and retrosternal pain 9 hrs. Myxoedema; left coronary thrombosis.	++	-	+	-	+	+	-	-	++	+
3444	M	57	R.V.hypert. Emphysema Gross obesity.	Pneumonia	-	-	Bronchitis for years. Early C.C.F.. Pneumonia and pulm. oedema.	-	+	-	-	-	-	-	-	-	++
3445	M	80	Cardiac amyloid.	Shock.	+++	+	Breathlessness and retrosternal pain 30 hours. Coronary atherothrombosis.	+++	+	+	-	-	-	-	-	++	++
3448	F	83	L.V.hypert.		+++	+	Paroxysmal nocturnal dyspnoea. Pain in upper abdomen 2 days. Died soon after admission. Left coronary atherothrombosis. Myocardial infarction.	+++	-	-	-	-	-	++	-	++	+
3455	F	75		Bronchopneumonia. Hb.9.6G%	+++	+	Acute mastoiditis, cervical abscess, faucial ulceration, lymphosarcoma. Atherothrombosis right coronary art.	+	+	++	++	-	-	-	-	++	++
3456	M	64	L.V.hypert.	Shock	+++	+	Acute retrosternal pain 3 hours. Left coronary atherothrombosis.	+	-	+	-	-	-	-	-	+	-
3457	F	75	Complete heart block	Shock.	+++	- Haem.into plaque of atheroma.	Severe retrosternal pain 24 hrs. Myocardial infarction.	++	-	-	-	-	-	+	-	+	+
3458	F	72	L.V.hypert.	Bronchopneumonia.	+++	+	Vomiting after meals 6 months. Ca. stomach; local spread.	+++	-	-	-	-	-	-	-	-	-

TABLE V cont.

3463	M	78	L.V.hypert.	Hb.4.3G%	-	-	Acute cystitis and lithiasis. Iron deficiency anaemia (old gastroenterostomy).	++	-	+	+	+	+	-	-	++	+
3470	F	75	L.V.hypert.		+++ Aortic stenosis	-	Dyspnoea on exertion for years. Admitted in gross C.C.F. Myocardial infarction.	+++	++	++	+	+++	+	++	+	+++	++
3473	F	72	L.V.hypert.	Hb.10.G%	+++	+	Breathlessness and angina one year. Coronary atherothrombosis. Myocardial infarction.	++	+	++	+	++	+	++	+	++	+
3476	M	90	L.V.hypert. R.V.hypert.	Emphysema Bronchiectasis. Bronchopneumonia.	+++	+	Admitted in C.C.F. Myocardial infarction; coronary atherothrombosis; bronchopneumonia and chronic pulm. disease.	+++	++	+	+	+	+	++	++	++	++
3480	F	80	Noradrenaline.	Shock.	+++	+	Dyspnoea on effort 3 yrs.; pain in chest (radiating down left arm) 12 hours.	++	+	++	-	-	-	++	-	++	-
3487	M	42	L.V.hypert. R.V.hypert.	Pulm. emb.	-	-	Subacute azotaemic nephritis. Influenza 3 weeks ago. B.P.150/94mm.Hg. Pulm.emb.	+	+	+	+	-	-	-	-	+	++
3491	M	78	L.V.hypert.	Shock	+++	-	Posterior gastro-enterostomy for pyloric stenosis. Post-operative death.	+++	-	-	-	-	-	-	-	-	-
3495	M	57	L.V.hypert.		+++	+	Angina 5 yrs.; severe pain in chest 36 hrs; myocardial infarction.	+++	++	+	-	-	-	++	+	++	+
3496	M	62	L.V.hypert.		++	-	Admitted 6 weeks before death. Acute myocardial infarction. Chest infection treatment - ulcerative colitis.	+++	++	++	-	+	-	-	-	++	-

TABLE V cont.

3502	F	75	Paget's disease of bone.	Pneumonia and apical T.B.	++	-	Cough and breathlessness 3 months; in C.C.F. Hodgkin's disease.	+++	-	+	+	-	-	++	-	+	-
3512	M	57	L.V.hypert.		+++	+	Angina pectoris 3 months Severe retrosternal pain off and on 2 weeks. Collapsed and died 3 hrs later. Myocardial infarction. Coronary atherothrombosis.	+++	+	++	+	++	+	++	-	++	+
3513	F	67	Moderate obesity.	Pulm.emb.	+	-	Breathlessness 3 months; urinary infection. Pulm. embolism.	-	-	-	-	-	-	-	+	-	++
3515	F	63		Multiple pulm. emboli.	+++	+	Diabetes 4 yrs. Secondary Ca. brain. Left common iliac thrombosis. Multiple pulmonary emboli.	++	-	-	-	+	-	-	-	-	-
3530	F	69		Anaesthetic. Pulm. emboli.	+++	+	Large bowel obstruction. Resection of colon and colostomy. Pulm. embolism.	+++	-	-	-	-	-	-	-	+	-
3533	F	47	Secondary Ca. myocardium	Bronchopneumonia. Hb. 11.6G%	-	-	Exenteration for Ca. cervix;- bladder fistula; transplant of ureters. Bronchopneumonia and abscess formation.	-	-	+	-	-	-	-	-	-	+
3537	M	53	Haemocromatosis.	Shock. Hb. 25%	++	-	Haemorrhage from oesophageal varices. Haemocromatosis. Myocardial infarction.	++	-	+	+	-	-	++	++	++	++
3541	M	67	R.V.hypert. L.V.hypert.	?virus pneumonia	-	-	Lower chest pain 3 weeks. Dyspnoea one month. Pneumonia.	+	-	-	-	-	-	-	-	-	++

TABLE V cont.

3561	F	79		Anaesthetic	+++	-	Bronchitis for years. Fracture of femur; post-operative death 2 hrs.	+++	-	-	-	-	-	-	-	+	+
3565	M	74	L.V.hypert. R.V.hypert.	Broncho-pneumonia.	+++	+	Appendicectomy; peritonitis; acute breathlessness 2 hrs. before death.	+++	+	++	+	+	+	-	-	-	+
3600	F	76		Hb. 4.16G%	-	-	Admitted in C.C.F. Died suddenly after transfusion. Pernicious anaemia	+	-	+	-	+	-	-	-	-	-
3602	F	66		Three anaesthetics	+	- (single coronary artery)	Diabetes. Sympathectomy for peripheral vascular idsease. 3 amputations. Fainted and died 14 hrs. later. Myocardial infarction.	+	-	-	-	-	-	++	-	+	-
3607	F	60	L.V.hypert. R.V.hypert. Obesity	Hb. 11.2G%	+++	+	Discharged 4 weeks ago after myocardial infarction. Paroxysmal nocturnal dyspnoea attack on admission, then "funny turn" and death 2 hours later.	+++	+	++	+	-	-	-	-	++	-
3610	F	79	L.V.hypert.		+++	- Giant cell arteritis.	Dyspnoea on exertion - months. Admitted in C.C.F. Myocardial infarction; giant cell arteritis (coronaries).	+	-	-	-	+	+	++	++	++	+
3626	M	38	L.V.hypert. R.V.hypert.	Hb.12.32G% Mult. pulm. emboli.	+++	+	Myocardial infarction 3 months ago. Pains in chest - multiple pulmonary emboli.	+++	+	++	+	+	+	-	-	-	-
3631	F	65	Leukaemic infiltration of myocardium.	Hb.3.84G%	-	-	Sub-leukaemic myeloid leukaemia (3 months).	-	-	+	-	-	-	+	-	-	-

TABLE V cont.

3689	F	74	L.V.hypert.	Hb.8.16G%	+	- Aortic stenosis and atheroma.	Angina for 5 years. Admitted with pain in chest which lasted 10 days before death. Acute myocardial infarction.	+++	+	-	-	-	-	+	+	+	+
3737	M	70	L.V.hypert. R.V.hypert.	Failure of resolution of pneumonia.	+++	-	Failure of resolution of acute lobar pneumonia. Acute retrosternal pain 18 hrs. Myocardial infarction.	++	-	-	-	-	-	++	-	+	-
3752	M	76	R.V.hypert. Cardiac amyloid.	Broncho-pneumonia	++	+	Dyspnoea on exertion - years. Chest pain 3-4 days. Myocardial infarction. Bronchopneumonia.	+	+	++	++	-	-	-	++	-	++
3773	F	33	L.V.hypert. R.V.hypert. Pulm. artery thrombosis.		-	- Aortic stenosis	Scarlet fever as a child; diphtheria at nineteen. Admitted in C.C.F. and jaundiced. Mitral, aortic and tricuspid stenosis. Cardiac cirrhosis.	+	+	++	-	-	-	-	-	-	-
3790	F	74		Lobar pneumonia	+	-	Admitted in C.C.F. with lobar pneumonia. Essential hypertensive.	+	-	++	++	-	-	-	-	++	+++

TABLE VI

Case No.	Sex	Age	Type and site of malignant disease	Sites of secondary involvement	Cardiac summary
3406	F	64	Aleukaemic leukaemia	Nil	Myocardial infarction. Hypoxic degn. Glycogenic degn.
3421	M	57	Ca. Bronchus	Intrathoracic lymph nodes.	R.V. hypertrophy. Hypoxic degn.
3426	F	69	Ca. Stomach	Peritoneal.	n.a.d.
3427	F	85	Glioma Cerebrum.	Nil	Fatty infiltration R.V. Interstitial fibrosis and focal myocytolysis R.V.
3443	M	76	Ca. Prostate	Nil	L.V. hypertrophy
3455	F	75	Lympho-sarcoma	Widespread	R. coronary atherothrombosis. Lymphosarcoma infiltration of myocardium. Focal myocytolysis and acute hypoxic degen. R.V. and L.V.
3458	F	72	Ca. Stomach	Nil	Healed myocardial infarction. L.V. hypertrophy.
3459	M	53	Ca. Stomach	Local spread.	Brown atrophy.
3460	F	67	Ca. Bladder	Nil	Moderate coronary atheroma.
3465	M	61	Ca. Pancreas.	Widespread	Secondary carcinoma.
3471	F	57	Ca. Rectum	Liver, lymph nodes, left ovary.	n.a.d.
3474	F	61	Ca. Breast	Peritoneum, pleura, vertebrae.	Secondary carcinoma
3475	M	63	Ca. Pancreas.	Liver, adrenals, lung, heart, lymph nodes.	Secondary carcinoma.
3478	F	75	Ca. Stomach	Lymph nodes, liver.	n.a.d.

TABLE VI cont.

3485	F	49	Ca.	Cervix uteri	Local	n.a.d.
3502	F	75	Hodgkin's Disease.		Generalised	Healed and acute infarction. Hypoxic degn. Focal myocytolysis.
3503	M	67	Ca.	Pancreas.	Nil	L.V. hypertrophy.
3505	M	49	Aleukaemic leukaemia.		Ileum, spleen, liver, kidney, brain.	Leukaemic infiltration.
3518	M	67	Ca.	Adrenal gland.	Lymph nodes and liver.	n.a.d.
3519	M	67	Ca.	Rectum	Nil	n.a.d.
3530	F	69	Ca.	Colon	Nil	Healed infarction. Coronary atherothrombosis (old). Acute hypoxic degn.
3533	F	47	Ca.	Cervix uteri	Regional lymph nodes and liver.	Secondary carcinoma. Focal myocytolysis. Acute degn.
3538	M	65	Ca.	Stomach	Nil	L.V. and R.V. hypertrophy.
3576	M	45	Aleukaemic leukaemia		Marrow changes only.	Auricular myocardial proteinosis.
3416	M	63	Ca.	Oesophagus.	Nil	n.a.d.
3627	F	75	Ca.	Uterus (body)	Peritoneum	n.a.d.
3631	F	65	Sub-leukaemic myeloid leukaemia.		Spleen, liver, kidneys and lymph nodes.	Fatty infiltration R.V. Acute infarction. Focal myocytolysis. Myeloid leukaemic infiltration.
3680	M	61	Seminoma	Testis	Widespread	n.a.d.
3710	F	70	Ca.	Colon	Nil	Coronary atheroma moderate to severe.
3749	F	59	Ca.	Colon	Peritoneum, liver.	n.a.d.
3781	M	63	Ca.	Rectum	Nil	n.a.d.

TABLE VII

Date	8.7.59	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	1.7	2	3	4	24	25	8.10
Resonium A dose/day (G)	nil	5	10	10	10	10	10	10	10	10	10	10	10	10	10	10	15	15	15	15	15	15	15	15	15	15	n i l		- 7.5 -	
Exp. rat R15		R ———																											— S —	
Pl KmEq/L	7.5		5.2	5.4	5.7		5.5	6.2	6.0	6.4	5.8							7.5				5.0					7.0-7.5		7.0-7.5	
Exp. rat R16		R ———																											— R —	
Pl KmEq/L	7.4		5.0	5.2	5.5	4.8	6.1	6.1	5.3	6.1					6.8	6.3		7.4				5.7					6.1-7.4		5.7-6.3	
Exp. rat R17		R ———																											— S —	
Pl KmEq/L	7.0			5.1	5.4	4.7	6.0		5.9	6.2	5.4				6.8	6.3		7.3				5.0					7.0-7.2		7.0-7.5	
Exp. rat R18		R ———																											— R —	
Pl KmEq/L	6.5			5.0	5.0		5.5	6.1	5.7	6.1	5.9	5.7			6.6	6.1	6.1					6.2					6.2-7.5		5.0-6.1	
Con. rat R7		S ———																											— S —	
Pl KmEq/L	7.5														7.5			7.0				7.5							6.6-7.1	
Con. rat R5		S ———																											— S —	
Pl KmEq/L	7.0														7.0			7.0				7.2							7.0-7.5	

R ——— "Resonium" A (Bayer)
S ——— Simple syrup (B.P.)

TABLE VIII

Date	25.6	8.7	5.10	7.10	14.10	23.10	30.10	6.11	12.11	24.11	3.12	15.12	20.12	31.12	6.1	14.1	10.4
R37	Chlorothiazide ———																killed
	Pl.K 6.0–7.0							Pl.K 6.4–7.0									
R38	Chlorothiazide ———																died
	Pl.K 7.0–7.4		DOCA					Pl.K 4.8–6.6									
R39	Chlorothiazide ———															killed	
	Pl.K 6.3–6.8		DOCA					Pl.K 5.15–5.9									
R40	Chlorothiazide ———														killed		
	Pl.K 6.5–7.1		Cortisone ———					Pl.K 5.0–6.6 ———									
R41	Chlorothiazide ———														killed		
	Pl.K 6.2–6.8		Cortisone ———					Pl.K 5.0–7.1 ———									
R42	Chlorothiazide ———													died			
	Pl.K 6.0–6.2																
R43	Chlorothiazide ———														killed		
	Pl.K 6.2–7.0																
R44	Distilled water ———														killed		
	Pl.K 7.0–7.4		Cortisone ———					Pl.K 4.8–7.0 ———									
R45	Distilled water ———														killed		
	Pl.K 6.8–7.2		Cortisone ———					Pl.K 4.9–7.0 ———									
R46	Distilled water ———														killed		
	Pl.K 6.7–7.0																

Note: Cortisone injected on dates above cont:-

T A B L E IX

Date	16.1.59	20.1.59	23.1.59	25.1.59	8.7.59	5.10.59	23.10.59	4.3.60	11.4.60	Body Weight (G)	Heart Weight (G)	Cardiac Index Ht. Wt: Body Wt. x 10^{-4}
R23	1% saline ———						killed			527	2.05	3.89
R24	1% saline ———				killed					538	2.15	4.00
R25	1% saline ———					DOCA		killed		550	2.25	4.09
R26	2% saline	Tap water ———				DOCA	Died			514	1.47	2.86
R27	2% saline	Tap water ———							killed	514	1.5	2.92
R28	2% saline	Tap water ———							killed	528	2.0	3.80
R31	2% saline	Tap water —Died								282	0.9	3.19
R32		1% saline ———							killed	327	1.49	4.56
R33		1% saline ———							killed	320	1.18	3.72
R34	2% saline	Tap water ———	Died							283	1.00	3.53
R35	Tap water ———								killed	282	0.9	3.19
R36	Tap water ———								killed	290	1.05	3.62

TABLE X

Experiment F.

Rat No.	Body weight (G)	Fresh heart weight (G).	Dry heart weight (G)	Cardiac Index	Treatment
48	220	1.15	0.31	5.23	Thyroid
49	416	2.00	-	4.8	Thyroid
50	215	1.20	-	5.58	Triiodo-thyronine.
51	380	1.54	-	4.05	Triiodo-thyronine.
75	225	0.80	0.27	3.55	Nil
76	395	1.20	-	3.29	Nil
77	205	0.72	-	3.51	Nil
78	398	1.10	0.31	2.76	Nil

TABLE XI

Experiment G.

Rat No.		Body Weight	Fresh heart weight	Cardiac Index	Haemoglobin levels (G%). 1.4.59	30.4.59	30.5.59	25.6.59
47	Horizontal	362	1.10	3.04	13.60	11.84	11.36	11.80
52	Horizontal	467	2.10	4.50	14.08	13.12	10.08	9.92
53	Horizontal	447	1.35	3.02	16.64	12.64	6.08	5.28
54	Tilted	437	1.53	3.50	15.68	9.92	5.92	5.92
55	Tilted	422	1.90	4.50	14.56	13.60	4.96	5.28
56	Tilted	362	1.18	3.26	16.00	13.60	11.36	11.80
57	Tilted	472	2.13	4.51	14.56	10.04	5.28	6.08
58	Horizontal	352	1.10	3.22	15.04	11.52	7.36	5.92
59	Control Horizontal	362	1.01	2.78	15.04	16.00	15.68	15.04
61	Horizontal	342	1.10	3.22	13.60	13.60	8.16	7.36
62	Control Horizontal	442	1.10	2.49	16.00	15.68	15.04	15.68
63	Control Horizontal	477	1.12	2.35	15.68	16.00	15.68	15.68
64	Control	362	1.01	2.78	13.60	15.68	15.04	14.80
65	Control Tilted	398	1.04	2.62	16.00	15.68	16.64	16.00
66	Control Horizontal	382	1.10	2.88	15.68	16.00	16.00	16.00
67	Control Tilted	365	1.01	2.77	14.08	15.04	14.08	14.80
68	Control Tilted	460	1.03	2.24	15.04	16.00	15.68	15.68

Statistical Analysis of Heart Weights in Experiments E, F and G.

	Experimental	Control
No.	16	21
Sum	60.49	61.63
Mean	3.781	2.935

Diff. = 0.846

$\therefore t = \frac{.846}{.189} = 4.4$

$\therefore p < .001$

TABLE XII

Case No.	Sex	Age (yrs)	State of imm.	Type of organism	Signs of cardiac involvement	Length of disease (days)
1	M	4	Yes		Marked bradycardia Slow gallop rhythm.	12
2	M	3	?		Nil	2
3	F	9	?	Gravis	Nil	9
4	M	5	No	Gravis	Sudden collapse after I.V. antitoxin.	3
5	M	3	No		Semicoma after antitoxin: died 8 hours later. Precordial pain.	4
6	M	3	No	Mitis	Glomerulonephritis. ?Cardiac failure.	17 (53rd day of scarletina)
7	F	2¾	No	Gravis	Pulse rapid and irregular. No signs of failure.	35
8	F	6	No	Gravis	Sudden cardiovascular collapse on the day before death.	16
11	M	5	No		Triple rhythm: peripheral circulatory failure.	25
14	M	12	No	Intermedius.	Congestive failure after 10 days.	14

TABLE XIII

Case No.	Sex	Age	Pulse/min.	Signs of Failure	Diagnosis	L.V. weight (G)	R.V. weight (G)	Cor. Ath.	Myocardial changes.
3388	M	68	150 irreg.	C.C.F.	Emphysema Infl. bronchopneumonia	155	105	++	Acute and healing infarction R.V.
3389	M	52	130 reg.	Cyanosed Breathless	Infl. bronchopneumonia	195	70	+ −	Nil
3392	M	39	120 irreg.	C.C.F.	Mitral and aortic stenosis. Bacterial endocarditis. Infl. bronchopneumonia.	110	80	+	Myocardial fibrosis Acute hypoxic degn.L.V.
3393	F	75	92 reg.	Nil	Infl. bronchopneumonia.	170	52	+ −	Inflammatory cell exudate. Acute hypoxic degn. R.V.
3397	M	63	108 reg.	Angina pectoris.	Infl. bronchopneumonia	390	95	+++	Old and acute infarction R.V. and L.V.
3399	M	52	80 irreg.	C.C.F.	Emphysema. Infl. bronchopneumonia	128	120	+ −	Acute infarction R.V.
3411	F	62	130 reg.	C.C.F.	Infl. bronchopneumonia	135	60	-	Acute hypoxic degn. R.V.